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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1951

ORIGINAL ARTICLES

THE LABORATORY DIAGNOSIS OF HYPERTHYROIDISM:

A Practical Analysis of Current Methods, with Presentation of Illustrative Cases

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The quantitative diagnosis of hyperthyroidism is based on laboratory techniques. While extremes of thyroid function are readily recognized clinically, the majority of thyrotoxic patients have only mild or moderate overactivity, and it is in the management of this group that the chemical and physical techniques recently developed have been most rewarding. The purpose of the present report is to examine critically the advantages and disadvantages of these several methods.

The following are laboratory techniques which have proved useful: 1. The basal metabolic rate (BMR). 2. The protein bound iodine level of serum (PBI)[4,12,13,14]. 3. The uptake of radioactive iodine by the thyroid gland[6,8,9,10]. 4. The rate of conversion of radioactive iodine into iodine bound by protein[4,5].

The Basal Metabolic Rate. The determination of the BMR, while not the most accurate or reliable method of measuring thyroid activity available, is certainly the most widely used. The test is easily, quickly and inexpensively performed by a technician in the physician's office. The equipment is compact, standardized, and lends itself to mass production. Nevertheless, it has several disadvantages. The most serious of these is that the test is only partially objective. Even when such conditions as a perforated ear drum, an ill-fitting mouthpiece or oxygen leaks in the system have been ruled out, the patient may find it impossible to achieve a truly basal condition. Benedict[3] has shown that an emotional disturbance may cause a marked increase in the BMR which may not subside for several days. The BMR may be performed under pentothal anesthesia as a means of securing basal conditions, but this is often not feasible.

A repeatedly normal BMR will rule

out hyperthyroidism in all but the very exceptional case, but a persistently elevated rate does not necessarily mean that the patient has thyroid overactivity. There are numerous other conditions which may be associated with an increase in the basal metabolic rate. Among these are acromegaly, leukemia, essential hypertension, certain drugs, pregnancy, infections, fever from any cause, polycythemia vera, and the administration of thyroid hormone. Since at times it may be impossible to exclude all these conditions, the limitations of the BMR are apparent.

Protein Bound Iodine Level of Serum. Since iodine was known to be an important component of the thyroxine molecule, it was reasoned[15] that the total blood iodine level might serve as a reliable index of thyroid function, but this did not prove to be the case. Total blood iodine was found to be affected by the daily intake of this element, and the correlation between the total blood iodine level and the level of thyroid activity was not dependable. However, Bassett, Coons and Salter[2] succeeded in fractionating the iodine of serum into its inorganic and organic components, and the organic component was found to exhibit a reliable direct correlation with the level of thyroid activity. This organic fraction has since been shown to represent the iodine of thyroxine and related compounds circulating in the blood stream. A carefully performed serum protein bound iodine determination is possibly the most accurate single measure of thyroid activity available, provided the patient has not recently received iodine compounds or thyroid hormone. It has the advantage of being a more objective determination than the BMR and is not affected by the numerous conditions that render the BMR unreliable. We have found the normal serum protein bound iodine level to range from 3.0 to 6.0 mcg. per 100 cc. of serum[7], and this agrees well with that obtained by other laboratories using the same method[4,12,14]. Values above this range indicate thyrotoxicosis; values below this range are found in myxedematous adults and in cretins. A real disadvantage of this method, however, is that it is a laborious chemical analysis that demands the time of a competent technician. In addition, the intake of iodine in any form renders the test suspect for a period of weeks or months, depending upon the compound in question. As an extreme example, the instillation of lipiodol for bronchography may cause a spurious elevation of the serum PBI level for as long as 15 months[11]. Nevertheless, if the serum PBI level is within normal limits, the patient almost certainly does not have thyrotoxicosis. This makes the test superior to the BMR in this connection, since a patient with a BMR of +15 may previously have had a BMR of −15, an increase in thyroid activity of 30 points for this particular individual.

Uptake of Radioactive Iodine by the Thyroid Gland. The availability of the radioactive isotope of iodine enabled Hertz, Roberts and Salter[10], and Hamilton[6] to employ the well known avidity of the thyroid gland for iodine as a measure of the level of thyroid activity. They demonstrated a direct correlation between the functional state of this organ and the amount of radioactive iodine stored there over a definite period of time. The normal range of uptake in humans was found to be between 10 and 40%. An uptake in excess of 50% was held to be specific for thyroid hyperactivity, but there was a slight overlap between the euthyroid and hyperthyroid patients. This test of thyroid function is now employed extensively in the larger clinics of this country and represents

a notable advance in our ability to diagnose thyroid disease.

The most serious deterrent to the general use of radioactive iodine is the somewhat elaborate and expensive apparatus required. The hospital must have available trained personnel, protective equipment, and instruments for measuring radioactivity. Many smaller institutions cannot afford these facilities. Aside from the expense involved in the use of the isotope, the uptake of radioiodine is affected by recently administered inorganic iodine and thiouracil compounds. Thyrotoxicosis resulting from the ingestion of thyroid hormone will not be detected by this method. Finally, if the goiter is partial intrathoracic the uptake of radioactive iodine cannot be determined accurately.

Conversion Ratio. During a series of investigations employing radioiodine as a tracer in the study of thyroid physiology, Chaikoff, Taurog, and Reinhardt[4] found that the rate of incorporation of radioactive iodine into protein by the thyroid was increased in rats and guinea pigs injected with thyrotropic stimulating hormone. These workers suggested that the rate of conversion of radioactive iodine into thyroxine might be used to measure thyroid activity. Clark, Moe and Adams,[5] found that the conversion ratio ranged from 13 to 40% in normal man. Those patients in whom the conversion ratio was 50% or greater were considered to have thyroid hyperactivity. We have obtained similar results in our laboratory[1]. If the conversion ratio has a definite advantage over the uptake of radioactive iodine as a measure of thyroid activity (and this is not yet fully established) it lies in the fact that the conversion ratio measures the actual rate of thyroxine formation and is not affected by the anatomical location of the thyroid tissue.

General Discussion and Illustrative Cases. It would be erroneous to imply that any one test of thyroid activity should be used to the exclusion of all others. On the contrary, the various procedures supplement one another. There are occasional patients in whom, if only one method is used, it is extremely difficult to determine whether thyroid disease is responsible for the increased metabolism observed. In these patients a combination of tests is most useful. For example, the overactivity of an intrathoracic goiter would not be diagnosed by a measure of the radioiodine uptake. The BMR would not be dependable if the goiter were large enough to cause dyspnea by tracheal compression. However, it might be evident from the increased conversion ratio and the elevated serum protein bound iodine level that the goiter was toxic.

Factitial hyperthyroidism due to the ingestion of excessive amounts of thyroid hormone would not be detected by a measure of the radioiodine uptake or by the conversion ratio alone, but it would be diagnosed when these studies revealed normal values in the presence of an increased serum protein bound iodine level and an elevated BMR. The following cases illustrate certain of these diagnostic problems.

Case 1. This obese 58-year-old white woman was admitted for excision of an anterior mediastinal mass which was presumed to be thyroid. Though her history was not particularly indicative of toxicity, she exhibited a suggestion of exophthalmus, a slight tremor of the hands, and mild heat intolerance. From the referring physician it was learned that the patient had been taking 6 grains of thyroid substance daily for the past 7 months in an effort to lose weight. Thus there arose a difficult diagnostic problem concerning the presence of thyroid overactivity. Was thyrotoxicosis present and, if so, was it due to true overactivity of thyroid tissue, or was it due to ingested thyroid hormone, or to both? The BMR was +39, but this was considered unreliable

because of the presence of dyspnea resulting from either cardiac failure or tracheal compression by the mediastinal mass. The uptake of radioactive iodine by the intrathoracic lesion was demonstrated, but because of its anatomical position an accurate estimate of its functional activity could not be made. The determination of the conversion ratio was unsatisfactory due to technical reasons. However, the PBI level of serum was 9.5 mcg. per 100 cc. This established the presence of a state of mild thyrotoxicosis, but this serum PBI level was considered to be compatible with the large dosage of thyroid substance which she had been taking. Thus while overactivity of the thyroid tissue could not be completely excluded, it did not appear likely, and this impression was verified by her clinical course. Operation was postponed 6 weeks to allow the state of induced hyperthyroidism to subside, and the mediastinal goiter was then resected.

COMMENT. In this case the BMR was rendered unreliable by cardiac disease. The uptake of radioactive iodine could not be measured accurately because of the intrathoracic position of the main mass of thyroid tissue and, even had this been possible, the test would not have indicated the presence of the excess of thyroxine derived from the ingestion of thyroid substance. Since the thyroid cells themselves were not hyperactive, the radioiodine uptake might well have been normal in the presence of an elevated serum level of thyroxine. The conversion ratio would have ruled out hyperactivity of the goiter, but would not have diagnosed the factitial hyperthyroidism. The elevated serum PBI level established the fact that the concentration of circulating thyroxine was increased, and this prompted the taking of a more detailed history which led to the diagnosis of factitial hyperthyroidism.

CASE 2. This 64-year-old white woman was admitted with a nodular goiter which had been present for 34 years. Her signs and symptoms did not definitely support the diagnosis of hyperthyroidism but the BMR was +45. The radioiodine uptake was 23%, a value within the euthyroid range, but the conversion ratio was 55%, indicating mild toxicity. A serum PBI level would have settled the issue, but the patient had received Lugol's solution. Nevertheless, a clinical trial of iodine therapy resulted in a prompt fall of the BMR to within normal limits.

COMMENT. This case represents the relatively mild type of thyroid overactivity often seen in elderly patients and previously described under such designations as atypical or apathetic hyperthyroidism. Here the BMR was suspect because of the presence of heart disease. The possibility of performing the test under pentothal anesthesia was considered, but the cardiac consultant advised against it. The values obtained by the radioiodine uptake and conversion ratio were not in agreement as to the presence of thyroid hyperactivity. The serum PBI level was rendered invalid by the administration of Lugol's solution. A therapeutic trial of iodine therapy established the diagnosis of hyperthyroidism.

CASE 3. This 30-year-old colored woman was admitted with a diffusely enlarged thyroid gland and clinical evidence of thyrotoxicosis. Eight months previously her BMR had been −19 and as treatment for sterility she had been placed on 2 grains of thyroid substance per day, a dosage which was maintained for 7 months almost without interruption. At the beginning of this therapy her thyroid gland had not been enlarged. Two months later, however, she began to tire easily and noted that her thyroid gland was increasing in size. Her BMR at the time of admission was repeatedly above +60. Likewise, her radioiodine uptake was 48% and the conversion ratio 69%. The serum PBI level was 12.0 mcg. per 100 cc. of serum, a value well within the toxic range. The consensus was that a mixed type of hyperthyroidism was present, and her subsequent course supported this diagnosis.

COMMENT. This case is an excellent example of the limitations of a single method used alone and is also illustrative of the value of employing a combination of diagnostic tests which measure different facets of thyroid

physiology. That this patient had an increased level of metabolism was suggested by the history, physical examination, and BMR. That the increased metabolism was due at least in part to an increased level of circulating thyroxine was established by the elevated serum PBI level. This last finding, taken together with the history of prolonged ingestion of thyroid extract, could easily have led to the diagnosis of simple factitial hyperthyroidism. However, the radioiodine uptake was 48% and the conversion ratio 69%, demonstrating hyperactivity of the thyroid cells. Thus the diagnosis of both factitial and true hyperthyroidism was made. This was an instance in which true thyroid hyperactivity developed while the patient was receiving thyroid extract.

Summary and Conclusions. 1. The advantages and disadvantages of several laboratory methods currently employed in evaluating thyroid activity are discussed.

2. These tests measure different facets of thyroid physiology, and thus tend to supplement each other.

3. Three representative cases illustrating specific diagnostic problems are presented.

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GASTRIC SECRETORY RESPONSE TO INSULIN HYPOGLYCEMIA: INFLUENCE OF INSULIN DOSAGE AND BLOOD SUGAR LEVEL

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Many workers have stated that the insulin test is of dubious value in the evaluation of vagus nerve function in patients having the operation, total vagotomy[10,11,12]. Others feel that it is a reliable test and that it has a definite place in determining the completeness of vagotomy[4]. Similar reports have appeared concerning gastric motility and insulin hypoglycemia[12].

Necheles and co-workers[7] stated that high doses of insulin and low levels of blood sugar caused a depression of gastric secretion in dogs in contrast to the expected stimulation. This work[5] has been quoted as one of the factors producing false negative results in the use of the insulin test.

The purpose of this present paper is to evaluate the gastric secretory response as influenced by large doses of insulin and low levels of blood sugar.

Methods. Nine psychotic patients undergoing insulin shock therapy were studied. Each patient had been receiving insulin shock treatments daily for approximately 2 months. Insulin dosage varied between 95 and 310 units of crystalline insulin administered subcutaneously. The period of study for each patient varied from 4 to 5 hours. A note of the depth of insulin shock was made at intervals. Specimens for blood sugar determinations were drawn prior to the administration of insulin and at 30 minute intervals thereafter. By means of a Levine tube, the stomach was emptied and two 15 minute specimens were withdrawn for controls. For the duration of the test period, the stomach was emptied every 15 minutes, the volume being accurate-

TABLE 1.—GASTRIC SECRETORY RESPONSE AS INFLUENCED BY DOSE OF INSULIN AND DEPTH OF HYPOGLYCEMIA

Case	Insulin dosage cryst. units subcut.	Character of insulin shock	Depth of hypoglycemia mg./100 cc.	Increase in gastric acid c.u. F.A.	Increase in gastric acid c.u. T.A.	Gastric aspirate avg. 15′ volume cc. Before acid response	Gastric aspirate avg. 15′ volume cc. After acid response	Macroscopic blood in gastric aspirate 0 + + + + +	Macroscopic bile in gastric aspirate 0 + + + + +
I	105	Precoma	27	31	41	12.1	15.1	+ + + +	0
II	110	Coma	19	6	17	2.8	8.1	0	+ + +
III	95	Coma	18	69	77	8.6	21.0	+ + + +	0
IV	165	Coma	12	36	45	5.0	16.1	+ + + +	+ + +
V	185	Coma	24	63	72	4.9	78.5	+ + + +	0
VI	140	Precoma	15	74	82	10.1	22.1	0	+ + + +
VII	310	Coma	20	0	11	12.3	16.6	+ + + +	0
VIII	95	Precoma	32	5	16	11.1	11.8	0	0
IX	240	Coma	22	0	0	—	—	0	+ +

c.u.—clinical units.

* Present address: Ann Arbor, Michigan

ly measured and a sample saved for analysis. The presence of bile and macroscopic blood was noted for each specimen.

Blood sugar determinations were performed according to the micro-Folin-Wu technique.

The gastric specimens were titrated with 0.1 N sodium hydroxide to an exact endpoint of pH 3.5 for free acid and pH 7.0 for total acid, utilizing a Leeds-Northrup potentiometer. This eliminated errors inherent in the use of dye indicator endpoints and obviated the base neutralizing ability of proteins present in gastric juice[2,13].

Results. Five patients (Nos. 1, 3, 4, 5, 6) showed a marked gastric acid response with an increase in total acidity varying between 41 and 82 clinical units. Three patients (Nos. 2, 6, 8) showed a slight to moderate increase in total acidity of gastric juice (11 to 17 cu.). One patient failed to show free or total acid in any of the specimens despite the blood sugar level varying between 24 and 38 mg. per 100 cc. for 4 hours.

No correlation was found between the depth of hypoglycemia and the magnitude of gastric acid response. A marked response was obtained with blood sugars as low as 12, 18 and 15 mg. per 100 cc. (45, 77 and 82 cu. of total acid respectively). The gastric secretory response occurred at varied levels of blood sugar (range 21 to 49 mg. per 100 cc.). The secretory response occurred between 60 and 75 minutes in 5 patients, following administration of the insulin. Three patients showed a response only after 105, 175 and 210 minutes. One patient followed for 5 hours showed an increase in gastric acid only after the blood sugar had remained below 55 mg. per 100 cc. for 2 hours.

Insulin dosage did not appear to affect the acid response of the stomach or the depth of hypoglycemia. A marked increase in total acidity occurred following 105, 96, 165, 185 and 140 units of crystalline insulin. However, a 240 unit insulin dosage in one patient failed to produce an increase in gastric acid.

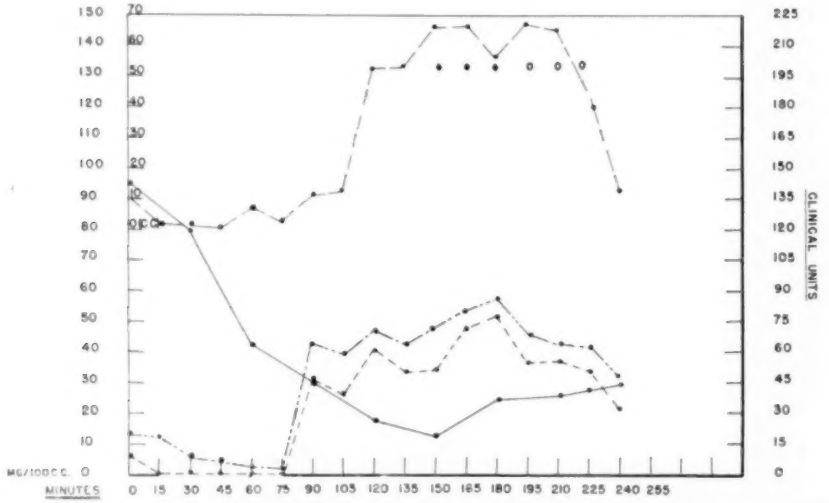

FIG. 1.—CASE 4: The gastric secretory response to insulin hypoglycemia in man as influenced by high doses of insulin and low levels of blood sugar.

The average 15 minute volume of gastric aspirate, after the acid response occurred, showed a slight to marked increase (range 0.7 to 73.6). However, many of the specimens contained large amounts of blood and bile and the significance of these findings cannot be evaluated.

Six of the patients studied were in deep coma for 1 to 2 hours, and all showed marked signs of insulin hypoglycemia such as restlessness, muscle twitching and marked perspiration.

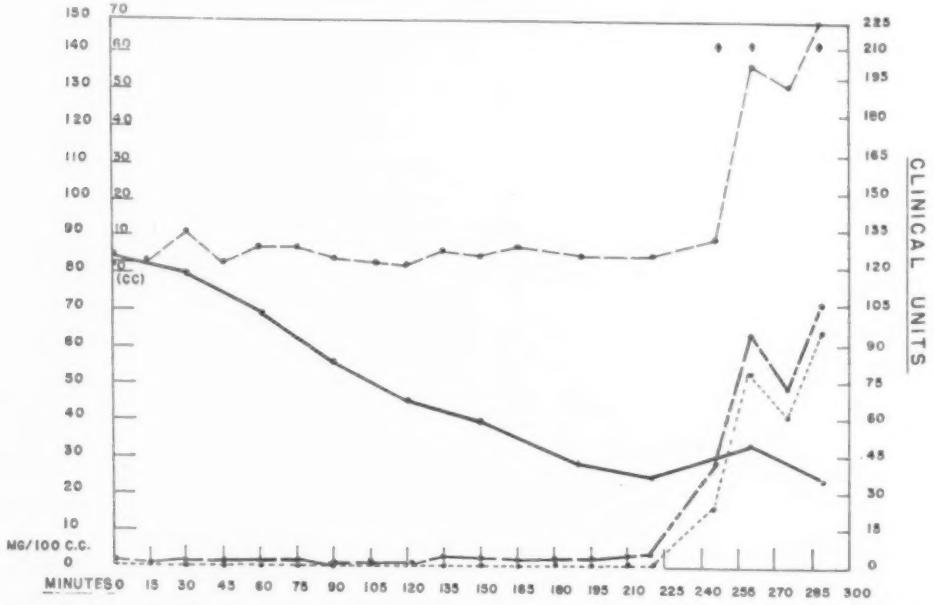

FIG. 2.—CASE 5: The gastric secretory response to insulin hypoglycemia in man as influenced by high doses of insulin and low levels of blood sugar.

In 5 patients, large amounts of hemolyzed and clotted blood were present in the gastric aspirate. This appeared and showed a progressive increase in amount, following the onset of the gastric secretory response. Similarly, moderate to large amounts of bile were noted in the gastric juice of 4 patients.

Discussion. Necheles and co-workers[6] showed that in dogs, the motility of the stomach varied with the depth of hypoglycemia following the subcutaneous administration of insulin. They found that at blood sugar levels of 10 to 23 mg. per 100 cc., inhibition of gastric motility occurred. Their results were explained on the findings of Quigley and Templeton[9] who showed that insulin hypoglycemia inhibited gastric motility following total vagotomy. They felt that this was due to stimulation of the unopposed sympathetic nervous system. It is believed that gastric motility and the psychic phase of gastric secretion are governed by the activity of the vagus nerves which are stimulated by insulin hypoglycemia[1]. It is reasonable to infer, therefore, that changes in gastric motility would be reflected in gastric secretion. Necheles *et al.* in a subsequent publication[7] found that in dogs "less stimulation of gastric secretion was associated with higher doses of insulin and lower levels of blood sugar." They found that severe hypoglycemia de-

pressed gastric secretion. However, it is significant that their experimental animals failed to show subjective signs of hypoglycemia.

In the present study, high doses of insulin and extreme hypoglycemia did not appear to depress the gastric secretory response. Five patients, despite 105, 95, 165, 185 and 140 units of crystalline insulin and a maximum fall of blood sugar to 27, 18, 12, 24 and 15 subjects in this study showed marked symptoms of hypoglycemia ranging from restlessness to profound coma.

The average dose of insulin in these 9 patients was 2.2 units per kg.; whereas Necheles *et al.*[7] used 0.5 to 0.7 unit per kg. in their animal experiments. The difference in their results and those recorded in this study may represent a species response different in man and dogs.

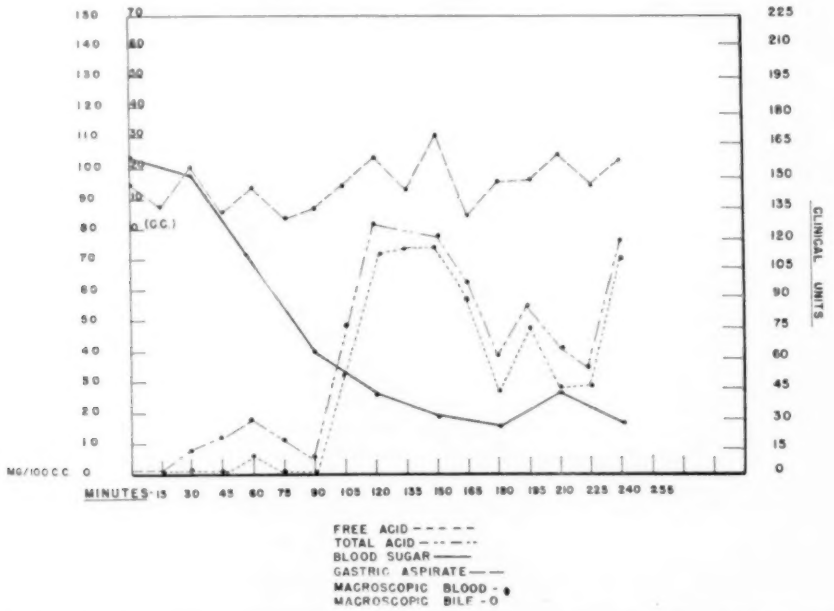

FIG. 3.—CASE 6: The gastric secretory response to insulin hypoglycemia in man as influenced by high doses of insulin and low levels of blood sugar.

mg. per 100 cc., respectively, showed a marked acid response. Three patients similarly receiving large doses of insulin and developing low levels of blood sugar showed a slight to moderate increase in gastric acid. The lack of acid response in 1 patient, despite a period of study for 5 hours and a hypoglycemia of 22 mg. per 100 cc., is unexplained since circumstances would not permit the performance of a triple histamine test to determine whether the stomach was capable of secreting acid. It is important to note that all

Quigley, Johnson and Solomon[8] have shown that gastric motility induced by insulin hypoglycemia is inhibited following the injection of adrenalin intravenously. Similar findings have been recorded by Wilder and Schlutz[14], and Quigley and Templeton[9]. It becomes readily apparent that the presence of an increased amount of circulating adrenalin modifies the gastric response to insulin hypoglycemia. Cannon, McIver and Bliss[3] have further shown that a discharge of adrenalin occurs when the blood sugar, after insulin, falls to

about 70 mg. per 100 cc. This latter fact may account for the depression of the gastric secretion that normally occurs prior to the point of stimulation during insulin hypoglycemia.

In the performance of the insulin test to determine vagus nerve function of the stomach, consideration should be given to the possible depressant action of circulating adrenalin on the stomach. For example, in an apprehensive patient or in a patient who is not tube-broken, exhibiting overt signs of sympathetic activity, the possibility of a false negative response due to circulating adrenalin should be considered. However, no concern need be had over the dose of insulin ordinarily administered in performing the insulin test (15 to 25 units). Likewise, the depth of hypoglycemia attained does not influence the gastric secretory response and there is evidence to indicate that the lower levels (40 mg. per 100 cc. or less) are associated with a more positive gastric response.

Attention should be directed to prolonging the period of observation (up to 4 hours) since in 1 patient a response was forthcoming only after the blood sugar had remained below 55 mg. per 100 cc. for 2 hours.

The insulin test of gastric secretory function must be conceded to be extremely sensitive, affected by many variables. Proper preparation and cognizance of interfering factors are essential to the interpretation of the results of the test. In any one patient, repetition of the test 2 or more times should tend to eliminate many of the borderline results so frequently obtained. The insulin test will have its chief value as an experimental test procedure. Clinical evaluation of a patient having total vagotomy will serve as the most reliable measure of the completeness of vagus section.

Summary. 1. High doses of insulin and low levels of blood sugar do not inhibit the gastric secretory response in humans.

2. The insulin test as employed clinically is extremely sensitive and affected by many variables. It chief value lies in its use as an experimental test procedure.

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VITAMIN D INTOXICATION*

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During the past 20 years, vitamin D and the irradiated sterols have come into wide and, at time, indiscriminate usage. In addition to the administration of vitamin D in specific deficiency states, massive doses (50,000 to 1,000,000 units daily for periods of days to as long as 3 to 4 years) have been used in attempted treatment of such conditions as pulmonary and cutaneous tuberculosis, scleroderma, various allergic states, and especially rheumatoid arthritis[1,31,32,37].

Accordingly, as early as 1930, there began to appear in the medical literature reports of varying degrees of toxicity from massive administration of vitamin D. Observers undoubtedly failed to recognize many cases of this syndrome; and the paucity of adequate chemical and Roentgen-ray data in the majority of cases described makes even extensive review of the literature but an approximate indication of the incidence and severity of hypervitaminosis-D. Within the past 20 years, there have occurred at least 5 deaths[23,24] attributed to vitamin D intoxication and several more in which this substance was implicated as a contributing factor[3]. Data available from a review of 111 cases described in the literature are summarized in Table 1.

It is the purpose of this paper to review and reëmphasize the clinical, chemical, tissue, and skeletal changes that occur in the syndrome of vitamin D intoxication; to report in detail 7 cases studied and treated within the past 3 years at this hospital; and to stress again the serious import of vitamin D as a toxic agent.

Occurrence. As is suggested above, the exact incidence of vitamin D intoxication is not known. There is obviously a wide variation in individual susceptibility; some patients display toxic symptoms on as little as 50,000 units per day for a few weeks, whereas others may tolerate 10 times that dosage for 6 to 12 months before manifesting toxic effects of the medication. High dietary calcium[17] and probably pre-existing renal disease predispose to early appearance and enhanced severity of intoxication.

Review of the multi-vitamin preparations available without prescription reveals that there are at least 2 brands containing as much as 50,000 units of vitamin D per capsule† and there is a greater number of high-concentrate

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† Darthronol (Roerig); Dalsol (U. S. Vitamins).

TABLE 1.—FINDINGS IN 111 CASES OF HYPERVITAMINOSIS-D REPORTED IN THE LITERATURE

				General									Urine					Chemical					
Name of Author	*No. of Cases*	*Sex*	*Age*	*Arthritis*	*Nausea, Vomiting*	*Weight Loss*	*G-U Symptoms*	*Headache*	*Weakness*	*Amount of Vit. D × 1000 u/day*	*Duration of Treatment*	*Spec. Gravity*	*Albumin*	*Casts*	*RBC*	*WBC*	*Hemoglobin gm. /100 cc.*	*Non-protein Nitrogen mg./100 cc.*	*Calcium mg./100 cc.*	*Phosphorus mg. /100 cc.*	*Alk. Phosphatase Bodansky Units /cc.*	*Phenolsulfonphthalein Excretion*
Tumulty	2	M	32	0	+	0	0	0		750	12 da.	1006		+	+		8.5	52	15.0	3.8		D
		M	12	0	+					750	17 da.	1008						45	18	2.9		D
Thatcher	1	M	1.5	0		+			+	CLO*	4 mo.		+	0	0	+			N	I		
Mulligan	1	M	44	0						?	?	1022	+	+	+	+						
Danowski	2	F	60	+	+					200	6 yr.	1013	0	0			8.5	67	15.3	4.5		D
		F	56	+	+	+				500	5 mo.	1005	+	+			9.0	55	14.5	5.2		D
Reed	43	M + F	7–72	+	+	+		+	+	300– 1000	10 da.– 3 yr.											
Vrtiak	20	M + F	23–66	+	+		+			150– 260	1 mo.– 12 mo.											
Hess	7	M + F	1	+	+				+	2.5 mg.**	1 mo.		+	+					I	I		
Jelke	1	F	1.5	0	+	+			+	900	7 wk.		+									
Pulschar	1	M	5	0	+	+				?	sev. mo.											
Rees	1	M	1	0	+	+				200								N	N	N		
Paul	5	F	50	0	+	+	+			150		1006							11	2.7		
		M	58	+	+	+	+			300		1012	+	+			11.5		12	3.1		
		F	49	+	+	+	+	+		400		1012	+				11	N	N	N		
		F	65	+	+					150		1002	+	+			8		13.5	5.7	5.0	
		F	38	+	+	0	0	0		150– 500									N	N	N	
Farley	5	M + F		+	+								+	+	+	+		I				
Thatcher	1	M	1.5	0	+	+				100– 500	1 yr.			+	+	+	8.0					
Bauer, J.	1	F	29	+	+	+	+	+	–	200	2 wk.						11.4		12.7			
Covey	5	F	66	+		+		+		350	2 mo.		+	+			12.0	I	11.5			
		F	54	+	+	+		+	–	50– 500	1 yr.	1010					10.0		13.0			
		F	45	+			+			200	6 mo.	1011	+	+		+		I				
		F	68	+	+			+		200	4 mo.	1011	+			+			12.5			D
		M	29	0	+	+				50– 150	3 yr.	1009	+				12.0	I	13.4	4.4	3	D
Donegan	2	F	59	+	+	+	+	+	+	150– 300	6 mo.	1009	+				10.0	I	13.0	2.2	4	D
		F	56	+	+			+	–	20– 300	5 wk.– 1 yr.								11.1– 16	5.1– 5.5	N	
Bauer, W.	12	M + F	28–65	+	10+		2+	1+		100– 500	1 yr.											
Freyberg	1	F	32																			
TOTAL	111																					

* Cod Liver Oil
** Ergosterol

D Decreased
N Normal
I Increased

pure vitamin D preparations in both liquid and capsule form containing over 50,000 units per usual dose.** Accordingly, it is not unlikely that considerable numbers of vitamin-habituated individuals may be taking toxic doses of vitamin D without benefit of medical surveillance.

However, it must be said that the chief occurrence of vitamin D intoxication is in those patients who are receiving massive doses prescribed by their physicians in attempted treatment of some particular disease condition. It is not the purpose of this paper to discuss whether such treatment should be discontinued, but rather to indicate that physicians who employ these potent vitamin D preparations should be alerted to the early signs of impending intoxication and aware of the clinical and chemical abnormalities associated with overdosage.

The Syndrome. The complete syndrome of hypervitaminosis-D has been repeatedly described and confirmed in the literature as consisting of the following:

1. *General:* weakness, fatigue, weight loss.
2. *Gastrointestinal:* nausea, vomiting, diarrhea, abdominal cramps.
3. *Neurological:* headache, paresthesias, vertigo.
4. *Psychiatric:* variable mental symptoms—depression, mild psychosis, stupor.
5. *Hematological:* normocytic, normochromic anemia.
6. *Urological:* albumin, red cells, casts in the urine, with progressive impairment in concentrating ability; frequency and nocturia.
7. *Ophthalmological:* band keratitis.
8. *Chemical:* elevated serum calcium and phosphorus, with normal or slightly elevated alkaline phosphatase. Progressive nitrogen retention.
9. *Roentgenological:* diffuse demineralization of the bones in advanced cases; periarticular soft tissue calcifications.
10. *Pathological:* Scattered calcium deposition in kidney, blood vessels, periarticular soft tissues, heart, stomach, lung, thyroid and pancreas.

Depending on the severity of intoxication, all or only a few of the above-described findings will be present, as indicated by the following case reports. Table 2 summarizes the specific laboratory and chemical data which are mentioned only generally in the case reports.

Case Reports. CASE 1. (*Unit No.* 610997. *Adm.* 3-26-48. *Disch.* 5-14-48.)

This was the first admission of a 65-year-old man. For 2 years prior to admission he had suffered from arthritis of the knees. During the greater part of this time, he had ingested 200,000 to 300,000 units of vitamin D per day in treatment of his arthritis, in addition to drinking 1 to 2 quarts of milk daily. Three months before admission, his arthritis became generalized, with most marked involvement of his shoulders, wrists, hands and cervical spine. In addition, during this interval he developed anorexia, marked weight loss, weakness, fatiguability, nocturia, and noted the appearance of non-tender fluctuant, periarticular masses in relation to his elbows, wrists, cervicothoracic spine, and several metacarpophalangeal joints.

There was no known history of previous renal disease.

Significant Physical Findings: Apathy, pallor, weakness and emaciation. Band keratitis. Senile pulmonary emphysema. Grade 2 apical systolic murmur without other significant cardiac abnormality. Blood pressure 145/60. Generalized moderately severe rheumatoid arthritis. Multiple 1.5 to 2.0 cm. soft, non-tender masses over the second metacarpophalangeal joints and ulnar and radial aspects of the wrists bilaterally. A similar 3 cm. mass was longitudinally situated over the lower cervical and upper thoracic spine. Benign prostatic hypertrophy.

** Actophen (Biochemical Research); D Vitamin Capsules (Squibb); D-Vatine (Dorsey); Davitin (I.V.C.); Decaps (Cole); Decolake (Lakeside); Dee-Ron (Warren-Teed); Dee-Osterol (Breon); Dee Ronal (Warren-Teed); Deltalin (Lilly); Deratol (Brewer); Hi Deratol (Brewer); Diactol (Plessner); Drisdol (Winthrop-Stearns); Ertron (Whittier); Infron Pediatric (Whittier); Super-Seal Vitamin D (Drug Products); Viderol Capsules (Parke, Davis); Vio-D (Rowell); Viosterol Concentrated (Merrell); Vitamin D Capsules (Abbott, Bristol, Lederle, Miller, Schieffelin, Sharp and Dohme, Sherman, Ulmer, Upjohn, U. S. Vitamin, Walker Vitamin, Wyeth).

Laboratory Data: Admission hemoglobin 8.0 gm. Urine specific gravity fixed at 1.012, moderate albuminuria, markedly impaired phenolsulfonphthalein excretion. Elevated serum calcium, normal to slightly elevated serum phosphorus and alkaline phosphatase, elevated serum non-protein nitrogen, increased 24 hour urine calcium excretion. Congo Red test negative. Roentgen rays revealed moderate generalized demineralization of bones, arthritic changes in joints, and opaque calcium-containing masses in the sites described under *Physical Findings.*

Course: During the early phases of the patient's admission, his condition deteriorated. Serum calcium and non-protein nitrogen rose for a time; he became weaker and more apathetic. One important obstacle to treatment was the patient's refusal to take an adequate fluid and caloric intake or to be mobilized from bed. He was given 3 transfusions of 500 cc. whole blood, and his oral intake was supplemented by Levine tube feedings. In addition, he received 5 mg. stilbestrol per day. Approximately 1 month after admission his clinical and blood chemical status began to improve; he became alert, stronger, and regained full ambulation. The periarticular masses slowly disappeared. No significant improvement in renal function occurred other than that secondary to improved hydration. Despite transfusions and ferrous sulfate, his hemoglobin was only 9.0 gm. at discharge.

Unfortunately, no follow-up is available as to his course after leaving the hospital.

CASE 2.* (*Unit No.* 617407. *Adm.* 5-4-48. *Disch.* 5-21-48.)

This was the first admission of a 55-year-old woman. She presented a 30 year history of progressive spondylitis and peripheral rheumatoid arthritis with resultant bed-chair invalidism. Three months prior to admission, after taking 300,000 units of vitamin D daily for 3 months, coincident with a diet high in calcium content, she had the onset of weakness, anorexia, progressive weight loss, and noted the appearance of soft, tender masses over her low back and in relation to her knees, wrists, shoulders, and scapulae. No history of previous renal disease was obtained.

Significant Physical Findings: Pallor, weakness, and emaciation. Band keratitis. Advanced, generalized rheumatoid joint changes. Soft, slightly tender, fluctuant 1.5-8.0 cm. masses at the base of the right thumb, over the right radial tuberosity, right scapulohumeral joint, inferior border of the left scapula, left sacroiliac joint, and medial aspect of the left knee. Blood pressure: 100/65.

Laboratory Data: Admission hemoglobin 7.5 gm. Urinary specific gravity fixed at 1.010, moderate albuminuria, markedly impaired phenolsulfonphthalein excretion. Elevated serum non-protein nitrogen, calcium, phosphorus, and slightly elevated alkaline

TABLE 2.—CHEMICAL VALUES IN THE 7 CASES HERE REPORTED

Patient	*Non-protein Nitrogen mg./100 cc.*	*Total Protein gm./100 cc.*	*Albumin/Globulin*	*Serum Calcium mg./100 cc.*	*Serum Phosphorus mg./100 cc.*	*Alkaline Phosphatase Bodansky U.*	*Phenolsulfonphthalein Excretion*	*Maximum 24 hr. Urine Calcium Excretion mg./24 hr.*
Case 1	48–28	7.32	1.2	15.2–11.6	5.5–2.8	6.9–3.9	D*	445
Case 2	65–49	6.24	2.2	13.4–12.6	5.7–4.7	7.1–5.5	D	283
Case 3	70–50	7.00	1.2	14.4–10.2	6.3–4.8	7.4–3.3	D	110
Case 4	84–44	7.48	1.1	13.0–11.2	5.5–2.8	7.0–4.0	D	160
Case 5	22–17	6.72	1.0	13.7–9.4	4.8–2.7	4.0–2.6	N**	527
Case 6	50–43	7.50		15.6–14.8	3.2–3.0	1.8	D	530
Case 7	46–37	6.69	1.0	12.6	3.7	3.3	D	

Where more than one value is known, the range of values is given
*D—Decreased
**N—Normal.

* This case is included in the "Case Records of the Massachusetts General Hospital" in the New England J. Med., 1950, in press.

phosphatase; normal to moderately increased 24 hour urinary calcium excretion. Roentgen rays revealed moderate generalized demineralization of bones, arthritic joint changes, and the cystic masses of calcium described above.

Course: With mobilization, low calcium diet, and forced fluids the patient's non-protein nitrogen, calcium, and phosphorus decreased, but did not reach a normal range. Alkaline phosphatase remained essentially unchanged. Her urinary calcium increased from a normal to a moderately elevated level. With 3 transfusions of 500 cc. whole blood her hemoglobin rose to 12.5 gm. She failed to tolerate stilbestrol because of nausea. The periarticular cysts decreased in size and became less fluctuant. No significant improvement in her renal status was apparent. She left the hospital against advice, much improved, but before full therapeutic results had been obtained.

Follow-up: Despite attempts at follow-up, contact with her was lost until almost 3 years later, when she was admitted terminally ill with jaundice, peritonitis, and uremia. Her serum calcium was below normal on this admission, and the previously described soft-tissue cysts had largely disappeared, though calcification in the soft tissues was clearly seen by Roentgen ray. She died after a brief period in the hospital.

Autopsy revealed widespread, generalized calcification. Her diagnoses included active disseminated pulmonary, renal, bladder and endometrial tuberculosis, Boeck's sarcoid in the lungs, nephrosclerosis and probable chronic pyelonephritis, chronic cholecystitis with multiple liver abscesses, perforation of the gall bladder, and generalized peritonitis. Calcium was found in the soft tissues, periarticular tissues, lungs, blood vessels, kidneys, liver, adrenals, mesentery and spleen. The parathyroids were small. It was the opinion of the pathologist that the calcification within the pulmonary alveoli, in the soft tissues and in the periarticular regions, was almost surely the result of hypervitaminosis-D, whereas the calcium deposits elsewhere could conceivably have resulted from her other coexisting pathological states.

CASE 3. *(Unit No.* 24992. *Adm.* 6-19-47. *Disch.* 7-31-47.)

This was the second admission of a 39 year old woman, who entered for study and treatment of her rheumatoid arthritis. At age 12 she suffered an illness consistent with Sydenham's chorea but without other coincident or subsequent symptoms of rheumatic fever. She presented a 23-year history of progressive spondylitis and peripheral rheumatoid arthritis, resulting within 10 years of onset in varying degrees of deformity in all joints. During the 5 years before admission (1942-1947) she took an average of 100,000 units of vitamin D per day. Her diet was not high in calcium content. During the last year of this interval she developed anorexia, weight loss, nausea and vomiting, nocturia, and very distressing paresthesias in the legs.

Significant Physical Findings: Pallor and emaciation. Advanced peripheral joint changes and spondylitis. Hepatomegaly[*] (liver edge palpable 3 fingers below the inferior costal margin in midclavicular line). Rheumatic heart disease, with moderate cardiac enlargement, mitral and aortic systolic and diastolic murmurs, good cardiac compensation without treatment. Blood pressure: 130/88. Psoriasis. Band keratitis.

Laboratory Data: Admission hemoglobin 8.0 gm. Urine specific gravity fixed at 1.012, marked albuminuria. Increased non-protein nitrogen, calcium and phosphorus; normal to increased alkaline phosphatase; normal urinary calcium excretion. Congo Red test positive. *Note:* The increased phosphorus reflects the particularly severe degree of renal involvement in this case (secondary probably to both vitamin D intoxication and amyloidosis). Roentgen rays revealed moderate, generalized demineralization of bones, metastatic periarticular and extra-articular calcification, and arthritic changes in joints.

Course: Because of the presence of an active duodenal ulcer, the patient was placed on a 6 meal bland diet. She was given aluminum hydroxide in an attempt to decrease phosphorus absorption. No significant change occurred in the level of her increased non-protein nitrogen or serum phosphorus. Her serum calcium actually increased. She did not receive stilbestrol. The hemoglobin level showed no persistent increase despite 2 transfusions of 500 cc. whole blood.

Follow-up: The patient had a subsequent admission (9-1-48 to 9-4-48) for treatment of an exacerbation of her duodenal ulcer. In addition she has been seen regularly at the M. G. H. Arthritis Clinic up to the present. By 11-13-49 her serum calcium had fallen to within normal limits and has remained such. However, her serum phosphorus and non-protein nitrogen remained elevated until 10-26-49, when these determinations were found to be within normal limits. Her hemoglobin has slowly risen to a level of 12 gm. Roentgen ray studies have revealed a de-

[*] Secondary amyloidosis.

crease in the amount of her periarticular calcification.

CASE 4. (*Unit No.* 8997. *Adm.* 12-6-47. *Disch.* 1-19-48.)

This was the fourth admission of a 70-year-old woman. She gave a 15 year history of generalized rheumatoid arthritis. Shortly prior to this admission, she took 150,000 units of vitamin D daily for 6 months. The calcium content of her diet during this time is not known. Toward the end of this period she suffered the onset of nausea, vomiting, diarrhea, anorexia, weight loss, weakness, mental depression, and nocturia. A diagnosis of vitamin D intoxication was made, and hospital admission for study advised. She was known to have had a chronic urinary tract infection since 1933, without, however, apparent impairment of renal function prior to this admission.

Significant Physical Findings: Pallor, senility, weakness, signs of recent weight loss. Arteriosclerotic heart disease with slight cardiac enlargement. An apical systolic murmur with thrill. Soft, aortic systolic murmur. Blood pressure 140/70. Senile emphysema. Advanced, generalized, peripheral rheumatoid arthritis. Rheumatoid nodule over the styloid process of the right radius. Band keratitis.

Laboratory Data: Admission hemoglobin was 9.0 gm. Maximum urinary specific gravity 1.014, moderate albuminuria and pyuria, markedly impaired phenolsulfonphthalein excretion. Increased serum non-protein nitrogen and calcium; slightly increased phosphorus and alkaline phosphatase; normal urinary calcium excretion (1 determination). Roentgen rays revealed moderate, generalized demineralization of bones and severe arthritic changes.

Course: A urinary tract infection (probably a B. coli chronic pyelonephritis) was controlled with sulfadiazine. Her non-protein nitrogen fell to within normal limits, and her levels of serum calcium and phosphorus showed a downward trend. No essential change in her renal function occurred. The hemoglobin level showed no change.

Follow-up: Following discharge, the patient was seen regularly in the clinic until July, 1949. The non-protein nitrogen remained moderately elevated, and albuminuria and pyuria, as well as nocturia and polyuria persisted. Otherwise, except for arthritis, she remained in fair health—ambulatory and alert. The patient was readmitted on 2-2-50 and died on 2-8-50. The cause of death was probably progressive cerebral thrombosis. At the time of admission her non-protein nitrogen was 37 mg., serum calcium 10.8, phosphorus 3.4, and phosphatase 4.2 units. A severe B. coli urinary tract infection was present.

Autopsy revealed no definite visceral or other extra-skeletal calcification other than that compatible with her age.

CASE 5. (*Unit No.* 631593. *Adm.* 9-14-48. *Disch.* 3-12-49.)

This was the first admission of a 36-year-old woman. Three years before admission she had onset of pain in her thoracic spine. Eight months later she developed fatigue and arthritis involving multiple peripheral joints. This exacerbation persisted up to the time of admission. Seven months before entry she took 300,000 units of vitamin D daily for 3 weeks. During the subsequent period, she continued to take vitamin preparations of unknown composition in unknown quantity. Her diet during this period did not contain excessive amounts of calcium. The toxic symptoms, consisting of anorexia, nausea, vomiting, diarrhea, and weight loss, ensued 3 weeks before admission.

Significant Physical Findings: Pallor and weakness. Impaired hearing. Grade 2 apical systolic murmur without other cardiac abnormality. Blood pressure 120/70. Moderately severe spondylitis and peripheral rheumatoid arthritis. Band keratitis.

Laboratory Data: Admission hemoglobin 10.0 gm. Maximum urine specific gravity 1.012, slight albuminuria, moderate pyuria, B. coli and B. pyocyaneus bacilluria, normal phenolsulfonphthalein excretion. Serum non-protein nitrogen normal; increased serum calcium, normal to slightly elevated phosphorus, normal alkaline phosphatase; increased urinary calcium excretion. Congo Red test normal. Roentgen rays revealed slight, generalized demineralization of bones and joint changes consistent with rheumatoid arthritis.

Course: By 10-20-48 the symptoms of vitamin D intoxication had subsided under treatment with forced fluids and low calcium diet. Serum calcium, phosphorus, and urinary calcium excretion fell to within normal range. The urinary tract infection cleared on sulfadiazine.

Follow-up: The patient was followed regularly in the clinic. Except for her arthritis, she remained well until the occurrence of a gastric ulcer in December, 1949. She was admitted to the hospital (2-2-50 to 3-8-50) for treatment of her ulcer, which healed uneventfully on a medical program. At the time of this admission, the hemoglobin was 14.0 gm., urinalysis normal, and serum calcium, phosphorus, and alkaline phosphatase within normal limits.

CASE 6* (*Unit. No.* 693324. *Adm.* 3-1-50. *Disch.* 3-10-50.)

This 40-year-old man was admitted with a provisional diagnosis of nephritis. The past history was not remarkable save for 2 episodes (at ages 14 and 20 years) of apparent acute nephritis lasting approximately 1 year on each occasion, and exhibiting albuminuria, cylindruria, and blood pressure elevation. During the 20 years prior to admission, however, repeated physical examinations and urinalyses failed to reveal any evidences of nephritis or hypertension.

For a period of 8 mos. prior to admission, he took 200,000 units of vitamin D daily in treatment for chronic bursitis of his right shoulder. His diet during this time was not high in calcium content. Three months before admission he experienced progressive weakness, fatigue, severe polydypsia and polyuria, without other manifestations of vitamin D intoxication.

Significant Physical Findings: Pallor and undernutrition. Blood pressure 160/92. No evidence of intrinsic cardiac disease. Bilateral, slight costovertebral angle tenderness. Band keratitis.

Laboratory Data: Admission hemoglobin 9.0 gm. Slight albuminuria, moderate pyuria without urinary tract infection, impaired concentrating ability (maximum 1.010). Moderately elevated non-protein nitrogen, markedly elevated serum calcium, normal phosphorus and alkaline phosphatase. Increased urinary calcium excretion. Roentgen rays of the skeleton were not remarkable except for calcification in the area of the right subacromial bursa.

Course: Despite the brevity of the patient's hospitalization, definite improvement was observed without treatment other than cessation of vitamin D ingestion, ambulation, and forced fluids. At discharge his fluid intake and output were slightly less than half the excessive values he demonstrated on admission. The non-protein nitrogen and serum calcium showed a downward trend.

No follow-up is available at the present time.

CASE 7. (*Unit No.* 696311. *Adm.* 4-17-50. *Disch.* 4-26-50).

This 48-year-old woman was admitted to the Medical Service in transfer from the Neurological Service, where she had been admitted for investigation of undiagnosed headache. She presented a 10 year history of mild, generalized, peripheral rheumatoid arthritis. For a 6 year period, terminating 4 months before admission, she had taken 50,000, or more, units of vitamin D per day. During the 10 months prior to admission she had suffered progressive weakness, fatigue, anorexia, post-prandial nausea and vomiting, weight loss of 44 lbs., severe frontal headaches, and nocturia 3 times nightly without other genito-urinary symptoms. It is of interest that early in her intoxication the nature of her symptoms was not recognized, and in an effort to relieve them, her physician switched to another, equally potent, preparation of vitamin D.

Significant Physical Findings: Emaciation. Minimal arthritic changes in multiple peripheral joints. Two small nodules (probably rheumatoid) over the extensor surface of the right elbow and one over the distal end of the right humerus. Liver enlarged 2 finger breadths below the right costal margin. Blood pressure 180/106.

Laboratory Data: Admission hemoglobin 10.0 gm. Urine specific gravity fixed at 1.014, minimal albuminuria, occasional granular and hyaline casts, and markedly impaired phenolsulfonphthalein excretion. Elevated serum calcium, with normal phosphorus and alkaline phosphatase, elevated non-protein nitrogen, increased 24-hour urinary calcium excretion, elevated bromsulfonphthalein retention, thymol turbidity 6.0 units, and cephalin flocculation 3 plus at 24 and 48 hours. Roentgen rays revealed minimal arthritic changes in elbows, knees, and hands, without generalized osteoporosis or metastatic calcification.

Course: The patient was treated with low calcium diet, forced fluids, transfusions, ambulation, and supportive measures for her arthritis. On this program she showed some symptomatic improvement and her non-protein nitrogen fell to within normal limits. Unfortunately, further follow-up is not available because of failure of the patient to keep her return appointments.

Comments. No correlation can be established relating the duration or severity of the arthritic disease in these patients to the development of vitamin D intoxication. Furthermore, although 1 patient had extensive secondary amyloidosis and 2 had coincident urinary tract infections, one cannot substantiate from the case data available the reasonable speculation that pre-existing renal disease might

* This patient, sent in consultation to Dr. F. Dennette Adams because of the constitutional and genitourinary symptoms, is to be reported in more detail by Dr. Adams at a later date.

predispose to the renal complications of vitamin D intoxication.

It is interesting that the 2 patients with a definite history of unusually high calcium intake during the period of vitamin D therapy exhibited the most severe intoxication, and were the only cases in our series that developed calcium-containing cysts. This aggravation of vitamin D intoxication by high calcium intake substantiates the work done in experimental animals by Harris[17]. Unfortunately, in none of our cases was the diet studied for its ash content, for in accordance with Gough's[15] work in animals, it might be anticipated that vitamin D intoxication would be aggravated by any alkaline ash diet.

It will be noted that 6 of the patients exhibited so-called "band keratitis", a lesion which is commonly associated with disturbed calcium metabolism in a variety of disease conditions[6,38]. Its regular occurrence in vitamin D intoxication is almost certainly due to the existence of hypercalcemia, and is in no way a specific finding related to the vitamin D compound itself.

Both of the most serious cases of vitamin D intoxication reported in this paper were remarkable for the demonstration of calcium-containing cysts. With rare exceptions (Paul[24]—1 case, Danowski[8]—1 case), this phenomenon has not been reported previously as part of the syndrome of vitamin D poisoning. It is difficult to know whether to classify it as a specific manifestation of vitamin D overdosage or to rank it along with band keratitis as a manifestation of disturbed calcium metabolism. In both of these patients the cysts were localized largely in the periarticular areas and in the vicinity of bursae. The cysts were not fixed to the skin, but seemed firmly attached to the underlying tissues. They were fluctuant, did not transilluminate, and varied from 1.5 to 8.0 cm. in diameter.

Biopsies of several of these masses were made; the following is a brief summary of a representative pathological report:*

"A portion of the tissue seems to represent the lining of a cyst, bursa, or joint cavity with an inner layer of cells resembling hyperplastic and hypertrophied synovial cells and an outer layer of dense, partially hyalinized connective tissue. This membrane is thrown into irregular folds and is involved by a diffuse granulomatous inflammatory process. The granulomatous reaction is of the 'foreign body' type with many giant cells which often appear to be centered about irregular granules which measure up to 20 micra in diameter. These granules stain like calcium with hematoxylin and like fibrin with Mallory's aniline blue, Mallory's phosphotungstic acid hematoxylin, and eosin methylene blue. They are present in all portions of the membrane, as well as in the cavity of the cyst."

The mechanism of formation of these cysts remains obscure. Although in our cases they were associated with underlying joint disease, similar cysts have been described in both primary and secondary hyperparathyroidism without significant coincident joint disease. Accordingly, it seems likely that these cysts are merely a manifestation, like band keratitis, of profoundly disturbed calcium metabolism and are not pathognomonic of vitamin D intoxication *per se*.

The material contained within the cysts could be readily aspirated through an 18-gauge needle and presented a milky, somewhat viscous appearance. The chemical nature of this material is of some interest. In 2 of our cases, calcium, phosphorus, and alkaline phosphatase determinations were made upon the fluid itself and upon the sediment centrifuged from the fluid. The calcium/phosphorus ratio

* Obtained through the kind cooperation of Dr. Peter Kulka, M.D., of the Department of Pathology, Harvard Medical School.

of the sediments in these cases was more than twice that present in bone, a finding at variance with Paul's[24] case, in which the calcium/phosphorus ratio was reported as identical with that of bone.

Differential Diagnosis. The problem of differential diagnosis is generally not a difficult one. The only conditions with which vitamin D intoxication would be likely to be confused are primary and secondary hyperparathyroidism. In these latter, the serum phosphorus will be either low (primary hyperparathyroidism) or considerably elevated (end-stage renal disease with accompanying secondary hyperparathyroidism) and the alkaline phosphatase will be considerably elevated. In vitamin D intoxication, on the other hand, the serum phosphorus and alkaline phosphatase are normal or only slightly elevated.

Prognosis. The prognosis in cases of vitamin D intoxication, although difficult to judge before treatment is instituted, may generally be considered favorable following prompt cessation of administration of the drug and early institution of the therapeutic measures indicated below. As previously noted, if intoxication has been severe it may result in death. If fatal outcome does not occur, some degree of irreversible renal damage may remain, usually manifested by impaired renal concentrating capacity and diminished phenolsulfonphthalein excretion. In most cases, the metastatic cysts, band keratitis, azotemia, hypercalcemia, anemia, and symptomatology will disappear over a period of weeks or months following institution of treatment.

Prevention. Physicians should employ this potentially dangerous medication only in disease conditions in which existing evidence indicates a reasonable rationale for usage. Fortunately, the syndrome of hypervitaminosis D is slow in its development and affords opportunity for the physician to detect intoxication early, before significant damage has occurred. It is the belief of the authors that the incidence of severe intoxication can be entirely eliminated if the following simple precautions are taken in all patients being given large doses of vitamin D.

1. The patient should be informed sufficiently of the nature of the toxic symptoms to permit voluntary cessation of treatment if these symptoms appear.

2. Routine urinalysis and hemoglobin determinations should be checked at least every two weeks during treatment.

3. Blood calcium determinations should be followed at monthly intervals.

4. If significant abnormalities are found in the course of the above measures, treatment should be discontinued, and more complete laboratory studies should be obtained in order to clarify the nature of these changes.

Treatment. The treatment of the syndrome of hypervitaminosis D is directed towards: *a*, cessation of vitamin D intake; *b*, reduction of serum calcium level by restriction of calcium intake and encouragement of maximum urinary excretion.

Accordingly, in this group of 6 patients the following program of treatment was evolved: 1, cessation of vitamin D intake; 2, strict low calcium diet; 3, avoidance of undue exposure to sunlight; 4, avoidance of alkali; 5, maximum mobilization of the patient; 6, sufficient fluids to insure a daily urinary output of at least 2000 cc.

Some of our cases received stilbestrol, 5 to 10 mg. daily, on the theoretical assumptions that: *a*, it might increase calcium deposition in bone by favoring osteoid formation[2]; and, *b*,

by increasing urinary citric acid excretion, there would be increased calcium excretion as calcium citrate.

Summary. 1. The characteristics of the syndrome of hypervitaminosis D have been described and data available on over 100 cases from the literature have been summarized.

2. Seven additional cases seen at the Massachusetts General Hospital within the past 3 years have been described in some detail, with emphasis upon the findings of band keratitis and metastatic calcium cysts. The histology of these cysts has been described as well as the nature of the Ca/P ratio of their contents.

3. Current methods for treatment of the syndrome are described.

4. In addition to the already available evidence regarding the inefficacy of non-specific therapeutic use of vitamin D, as in most of the conditions listed earlier in this paper, special stress is laid upon the hazards of such therapy. If vitamin D is used in massive doses, it is pointed out that careful follow-up is obligatory for the early detection of the clinical and laboratory manifestations of intoxication.

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THE SERUM LIPIDS IN LIPEMIA RETINALIS

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Lipemia retinalis is an uncommon observation in patients with diabetic acidosis in which the retinal findings are believed to be due to an abnormal amount and proportion of serum lipid fractions. To date there have been 63 cases recorded in the literature[5,7,8,9,11,12,13]. All case reports bear out the following facts: 1) Most patients have been diabetics[13]. 2) The great majority of patients have been young males[11]. 3) All patients have been in true acidosis or have had some decrease of CO_2—combining power of the blood serum, presumably metabolic in origin. 4) The retinal picture is the only diagnostic physical finding. 5) The presence of lipemia does not alter the immediate prognosis for recovery from acidosis.

The retinal picture once seen is unmistakable. The arteries and veins are indistinguishable. Both appear as salmon-pink to chalky white, ribbon-like structures traversing the retina. These findings are transient and disappear within 48 hours in some cases.

An outstanding finding in lipemia retinalis is the appearance of the blood samples drawn from these patients. If the blood is allowed to stand and the cells sediment, it will be noted that a thick milky-white cream-like substance appears instead of a clear specimen of serum above the cells (Fig. 1). This serum, because of its high content of fat and its gross resemblance to fatty substances in general, has been termed "lipemic", as contrasted to clear serum which is termed "non-lipemic". However, the term "non-lipemic" applies only to the gross description of the serum and not necessarily to the lipid content of the serum, for indeed many specimens may contain greatly increased quantities of lipids and still be clear or "non-lipemic".

Ahrens and Kunkel[1] have recently investigated many cases of hyperlipemia in which the serum was either lipemic ("milky") or non-lipemic (clear). These studies were performed in the cases of nephrosis, congenital hyperlipemia, and obstructive biliary cirrhosis. In all except the last condition, the serum was lipemic. These workers emphasized that the proportion of phospholipids in the lipid makeup of the sera of these patients was the determining factor for the appearance of lipemic or non-lipemic serum.

It will be the purpose of this paper to re-evaluate the serum lipid fractions in another hyperlipemic state, lipemia retinalis, in an attempt to account for the presence of milky serum.

Although there are over 60 cases of lipemia retinalis described in the literature, there are few reports with com-

plete determinations of the various lipid fractions. We were able to find only 4 adequately studied cases[6,11], and have added 1 more. The serum lipids of these 5 cases have been re-evaluated in the light of Ahrens' work on the stabilization of serum lipid emulsions by phospholipids.

FIG. 1.—Blood specimen of Patient N. W. drawn on admission. Note "milky" condition of serum above settled red cells.

The following case is listed, as it presents all of the characteristic findings in lipemia retinalis.

Case Report. N. W., a 28-year old white male, was admitted to the Men's Metabolic Service of Dr. E. S. Dillon at 4 A. M. on June 25, 1950. History from his mother revealed that the diagnosis of diabetes mellitus had been made 2 months previously by his private physician. The patient refused to take insulin and attempted to manage his diabetes with diet alone. This latter regimen did not prove successful and the patient continued to lose weight despite a good appetite. Several days before admission he contracted a respiratory infection which in a matter of days led to mental obtundity and finally to semi-coma.

Physical examination revealed a semi-comatose white male with Kussmaul's respirations. Acetone odor was detected. His ocular tension was not palpably decreased. Signs of bronchopneumonia were detected at the right lung base. Other than a simple tachycardia the heart was thought to be normal. His temperature was 99°F. rectally. Blood pressure was 130/74. No xanthomatous skin lesions were noted.

Ophthalmologic examination, confirmed by an ophthalmologist 4 hours after admission, revealed: "Fundus O.D.: Media clear. Disc of distinct outline, normal cup, definite pallor. Veins somewhat overfilled. Both arteries and veins show a more or less salmon color instead of the normal red. Away from the disc the arteries and veins are difficult to distinguish from one another. Both appear somewhat flattened in the periphery. The fundus is pale with macular area more prominent in color than is normally seen. No hemorrhages or exudates noted. O. S. as O. D. Impression: "lipemia retinalis."

The initial blood studies, which showed the obviously lipemic serum were: Sugar: 380 mm.; CO_2—combining power 11 vols. %; hemoglobin 12 gm.; leukocytes 12,600; for fat studies see Table 1. The examination of the urine on admission showed: S. G. 1.024; 1+ albumin; 4+ sugar and 4+ acetone.

Therapy was rather vigorous because of the development of metabolic vascular shock and hypopotassemia following initial therapy (Serum K=3.0 mEq./l). In 58 hours' time the CO_2—combining power had risen to 51 vols. %, and his clinical picture was such that recovery was assured. During this period, he had received 875 units of regular insulin, 1000 cc. of 5% glucose in saline intravenously, 2000 cc. of 10% glucose in water intravenously, 1750 cc. isotonic sodium chloride by subcutaneous clysis, 500 cc. of blood, 500 cc. of 1.14% potassium chloride intravenously, and 1850 cc. of 1.14% potassium chloride subcutaneously.

He was then standardized on a diet of 220 gm. of carbohydrate; 110 gm. of fat; and 80 gm. of protein. His insulin dose on discharge was 32 units of protamine-zinc

insulin and 20 units of regular insulin in the morning.

His serum, which initially was milky (Fig. 1), cleared gradually, and 7 days following admission there was no longer visible evidence of lipemia.

METHODS AND CALCULATIONS. The blood lipid determinations were performed on fasting blood samples. The phospholipids were determined by a modification of Youngburg's Method[14]. The result of this determination was multiplied by the factor of 25 to convert milligrams of lipid phosphorus to milligrams of phospholipids.

The Man modification of the Stoddard and Drury[10] method was used for the determination of total fatty acids. This result is expressed in millimoles per liter. Multiplication by 269 and division by 10 converted millimoles to milligrams per 100 cc.

With the above figures the values for neutral fats and total lipids were calculated. The neutral fats were calculated by means of the Blood formula[3]. This states that the neutral fat equals the total fatty acids minus two-thirds the sum of cholesterol esters and phospholipids. The total fat figure was arrived at by the addition of phospholipids, total cholesterol and neutral fat values.

The figures listed from the case reports of Marble and Smith and from Herbert's 2 cases are as recorded in the original papers. The various methods used are not listed here. However, the ranges of figures are comparable with the data found in our patient and in other hyperlipemic states, and we therefore feel that the difference in methods does not alter the basic interpretation of this paper.

Results. In Table 1 are listed the concentrations of the serum lipid fractions of Patient N. W., and 4 cases derived from the literature, when the serum was "milky" or lipemic. It will be noted that in all 5 cases there is a marked increase in the total lipid content of the serum. Although this increase is due to an increase in all lipid fractions, by far the greatest increase is in neutral fat. The neutral fat fractions of the cases of Marble and Smith, and those of Herbert, were not listed in the original papers, but were calculated approximately here by the subtraction of the sum of phospholipids and cholesterol from the total blood fat figure.

Although the phospholipids were increased in all cases, it will be noted that of all the fat fractions they increased the least. This relatively small increase in phospholipids with the much greater increase in total fat, reduced the phospholipid/total fat ratio significantly. The normal phospholipid/total fat ratio found in our laboratory is 0.43. This checks closely with the normal values given elsewhere[1]. However, in none of the 5 cases of lipemia retinalis was the ratio greater than 0.10 and in one case was as low as 0.04.

In the last column is listed the phospholipid and total cholesterol ratio (P/T.C.). Although it is not the purpose of this paper to discuss this relationship at length, we wish to call attention to the fact that in Herbert's 2 cases, where xanthomatous lesions were present, this ratio was extremely low.

In Table 2 are listed the serum lipid fractions of 3 of the 5 cases, after the

TABLE 1.—THE SERUM LIPIDS IN LIPEMIA RETINALIS†

Case	*Total fat (mg./100 cc.)*	*Total fatty acids (mg./100 cc.)*	*Cholesterol total (mg./100 cc.)*	*Cholesterol esters (mg./100 cc.)*	*Phospholipid (mg./100 cc.)*	*Neutral fats (mg./100 cc.)*	*P/T.F.**	*P/T.C.***
Normal	573	376	200	140	250	123	0.43	1.2
N. W.	7,268.5	6,544	858	585	767.5	5,643	0.10	0.89
Marble & Smith No. 1	7,530	6,748	787	490	825	(5,898)	0.10	1.0
Marble & Smith No. 2	14,103	12,430	1,596	1,275	1,150	(11,357)	0.08	0.72
Herbert No. 1	22,000	—	1,410	—	950	(19,640)	0.04	0.67
Herbert No. 2	9,590	—	1,440	—	740	(7,410)	0.08	0.51

* P/T.F. is phospholipid/total fat.
** P/T.C. is phospholipid/total cholesterol.
N. W. case reported in this paper.
The neutral fat figures in parentheses were calculated from the published data of Marble and Smith, and Herbert.
† Records the serum lipid fractions in the lipemic ("milky") serum of lipemia retinalis.

serum had cleared. There were no follow-up figures available in Herbert's 2 cases. It can now be seen that the total lipids and other fat figures are practically normal. The decrease was most marked in the neutral fat fraction. There is noted a slight lag in the phospholipid return to normal. It can readily be seen that the phospholipid/total fat ratio is normal in all three cases, whose serum is now clear. The interval between the results of Tables 1 and 2 in the case of N. W. was 14 days, whereas the interval for the cases of Marble and Smith was 6 months and 2 months respectively.

lipids, which is most responsible for this normal non-visualized state of colloidal suspension, is the phosholipid portion. Phospholipids, the most soluble of the lipid fractions, act as emulsifying agents and maintain cholesterol, cholesterol esters, neutral fats in colloidal suspension. Boyd stressed the importance of the phospholipid/total fat ratio and found that a fall in this ratio below normal was correlated with the appearance of lipemic ("milky") serum. Ahrens recently has confirmed this viewpoint and attributes the solubilizing influence of phospholipids on the other fat fractions to its

TABLE 2.—THE SERUM LIPIDS AFTER RECOVERY FROM LIPEMIA RETINALIS†

Case	*Total fat (mg./100 cc.)*	*Total fatty acids (mg./100 cc.)*	*Cholesterol total (mg./100 cc.)*	*Cholesterol esters (mg./100 cc.)*	*Phospholipid (mg./100 cc.)*	*Neutral fats (mg./100 cc.)*	*P/T.F.**	*P/T.C.***
Normal	573	376	200	140	250	123	0.43	1:2
N. W.	937	670	281	209	375	281	0.40	1:3
Marble & Smith No. 1	569	358	193	141	250	(126)	0.43	1:3
Marble & Smith No. 2	836	648	175	120	325	(336)	0.38	1:9

* P/T.F. is phospholipid/total fat.
** P/T.C. is phospholipid/total cholesterol.
N. W. case reported in this paper.
The neutral fat figures in parentheses were calculated from the published data of Marble and Smith, and Herbert.
† Records the serum lipid fractions after the disappearance of lipemia retinalis when the serum is clear.

Discussion. There are normally 4 different lipid fractions in human serum. These are: free cholesterol, cholesterol esters, neutral fats and phospholipids. The last substance is a lecithin and is the main extracellular lecithin. The sum of the above 4 fractions constitutes the total fat value or total lipids. All of the above substances, except free cholesterol, contain a certain amount of fatty acids in their makeup. The amount of fatty acid released from the hydrolysis of these compounds is referred to as total fatty acids.

Normally the above compounds occur in definite proportion. Their normal colloidal and invisible state is maintained by virtue of the fact that the particles do not occur in sufficient size to be visualized by the naked eye. Boyd[4] has shown that the fraction of

strong surface actions. By means of this surface action, the phospholipids adsorb the various other fatty substances and prevent their coalescence to visible-sized particles. Hence, as long as the normal proportion between phospholipids and total fats is maintained, the solubility of the fats and therefore the clearness of the serum is assured.

As has been stated, Boyd considered the P/T.F. (phospholipid/total fat) ratio to be the determining fact of the presence of milky serum. He also calculated the ratios of other serum lipids and concluded that these were not important in predicating the state of the serum. The "milky" sera reported herein all contained elevated neutral fats. However, milky sera with normal neutral fat contents have been described[1]. Therefore, it cannot

be argued that the mere elevation of the neutral fat fraction is the cause of "milky" sera. In every case, however, the phospholipid/total fat ratio has been depressed.

Ahrens and Kunkel[1] have expanded the above work and verified the importance of phospholipids in the maintenance of serum lipid emulsions. Later Ahrens[2] published a series of results on the lipid fractions in 3 hyperlipemic states: namely, nephrosis, obstructive biliary disease, and congenital hyperlipemia. In only 1 of these 3 conditions, obstructive biliary disease, are the phospholipids increased proportionately to the increase in total fat, and hence the normal P/T.F. is preserved and the serum remains clear or non-lipemic.

We have here recorded another hyperlipemic state, lipemia retinalis, which is associated with a grossly milky or lipemic serum and which again illustrates the importance of the P/T.F. ratio. It can be seen from Table 1 that all the lipemic sera had greatly decreased P/T.F. ratios. In Table 2 are the available follow-up figures on 3 of these cases after the serum had become clear. This second group of figures records a normal P/T.F. ratio and hence the clearness of the serum appears accounted for.

We did not note any xanthomatous skin lesions in our cases. However, in both of Herbert's cases these lesions were noted, and, interestingly enough, these 2 cases had the most distorted or lowest phospholipid/total cholesterol ratio (P/T.C.) This ratio is the one which Ahrens believes is of importance in predicting the presence or absence of xanthoma and atherosclerotic lesions. We record this incidental fact because it adds further support to the belief that it is the proportion and inter-relation of the various lipid fractions which may account for the abnormalities in atherosclerosis, hyperlipemia, xanthoma, and others, and not the level of any one fraction.

Summary. 1. The clinical findings and the serum lipid fractions present in lipemia retinalis are reviewed.

2. All serum fat fractions, neutral fat, cholesterol, cholesterol esters, and phospholipids are elevated in this condition.

3. The phospholipid fraction, however, is elevated least. Thus the phospholipid/total fat ratio is depressed. It appears that it is this depression which allows fat particles to conglomerate to visible size and thus render the serum lipemic ("milky").

4. Follow-up studies reveal that the phospholipid/total fat ratio is normal when the serum is non-lipemic (clear).

5. The phospholipid concentration is an important factor in the maintenance of the other lipid fractions in solution in the serum.

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THE ROLE OF THE KETONE BODIES IN THE ETIOLOGY OF DIABETIC COMA*

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THE clinical entity of diabetic acidosis and coma has been recognized for more than a century and has been studied extensively for more than 60 years, yet today there is still no general agreement as to the specific cause of the coma that results from uncontrolled diabetes mellitus. This state of affairs is surprising and perhaps unique, considering not only the amount of work and thought given this subject but also the great advance in the understanding of the metabolic derangements in the diabetic state which has led to the present competent treatment of the diabetic patient. The diversity of opinion regarding the cause of the coma in diabetes results from the mass of conflicting experimental data which mirrors the complexity of the subject. A review of the literature is presented here in an attempt to evaluate previous experimental studies and classify conclusions reached. In addition, new evidence from studies of the diabetic patient and of the laboratory animal are presented in an attempt to answer the question: What is the cause of coma in uncontrolled diabetes?

Complete review of the literature is almost impossible. Several excellent reviews have been presented within the last decade[3,26,32,40] in which the broad aspects of ketosis and ketone body metabolism are discussed. In this paper, only the possible causes of the coma in diabetic acidosis will be considered, with particular reference to the question of specific toxicity of the ketone bodies, this term to include acetoacetic acid, β-hydroxybutyric acid and acetone. Experimental evidence is presented on the one hand, opinions on the other. In addition, direct evidence from the laboratory is presented separately from clinical observations of the derangements apparent in the human diabetic state.

1. THE ROLE OF ACIDOSIS IN THE PRODUCTION OF DIABETIC COMA. Naunyn, in the middle of the 19th century, first proposed the hypothesis that acidosis *per se* was the cause of coma in uncontrolled diabetes mellitus. Salkowski[35], in 1873, was one of the earliest to perform experiments on rabbits using phosphoric and dilute sulfuric acids and taurine, though he presented no conclusions from his work. Stadelmann[33], in 1883, subscribed to Naunyn's view and hoped to cure coma with the use of alkalis. Minkowski[33] also shared this view but mentioned the possibility of some other specific toxic effect. Walter[43], in 1887, observed that the administration of hydrochloric and phosphoric acids to rabbits caused coma and death without any gross pathological changes apparent at postmortem examination. He concluded that acidosis caused death and that the effects were completely reversible with the use of alkalis. Magnus-Levy[27],

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in 1911, was of the opinion that acidosis, probably caused by β-hydroxybutyric acid, was the cause of coma and death in diabetes. He presented no evidence here, and it is particularly interesting to note this conclusion in the light of his observation that "it must be conceded that only a few cases are known in which an advanced diabetic coma has disappeared under the use of bicarbonate of soda, in contrast to the absolute efficiency of alkalis in the case of the rabbit". Allen and Wishart[1], in 1923, and Schneider and Droller[36], in 1938, confirmed the toxic effects of acidosis in the rabbit, though they viewed this as a potentiating factor in diabetic coma and not the primary cause. Most recently, Peters and Van Slyke[32], in 1946, incriminated the acidosis itself as a very important factor when they stated that the acidosis plus nonspecific factors was the cause of shock, coma and death.

Wilbur[44], in 1904, gave β-hydroxybutyric acid and its neutral sodium salt to rabbits intravenously causing dyspnea, somnolence, convulsions, coma and death in a manner not duplicated by equivalent doses of hydrochloric acid. He thus concluded that diabetic acidosis symptoms are not solely due to lack of alkali. This type of experiment has been confirmed frequently with similar conclusions[1,14,21,29,36,42].

2. Direct Evidence Supporting the Hypothesis of Primary Ketone Toxicity. Allen and Wishart[1] have reviewed the very early experiments. From these and more recent investigations, including some presented in this paper, it is evident that acetone can cause toxic effects, but apparently only in amounts far greater than those encountered in human diabetic acidosis. Wilbur[44], in 1904, gave intravenous infusions of β-hydroxybutyric acid and its neutralized salt at a constant rate to rabbits. The exact amount was not specified. He produced convulsions and death, and concluded that in rabbits β-hydroxybutyric acid and its neutral sodium salt are toxic and cause symptoms similar to acidosis. Marx[1] caused coma in puppies, using 6 gm. of sodium butyrate intravenously and intraperitoneally. Dakin[10], in 1910, gave 10 gm. of sodium acetoacetate to a puppy weighing 3 kg., causing death in 4 hours. Ehrmann *et al.*[14], in 1911, produced coma in rabbits using 3.2 to 3.6 gm. of β-hydroxybutyric acid per kg. of body weight by mouth and intravenously. He produced similar results with the ethyl ester of butyric acid. Sodium isobutyrate did not cause symptoms unless the amounts were doubled, despite the fact that the blood alkali reserve was of the same magnitude in that experiment and was higher in the experiment where the toxic effects were due to butyric acid rather than the mineral acids. He concluded that the toxicity was due specifically to the butyric acid and not to the acidosis in this experiment. Hurtley[22], in 1916, experimented with the ketone bodies on decerebrate animals and showed specific effects on the posterior corpora quadrigemina. Others[17,41] showed them to act on the respiratory center. Tschun-Nien[42], in 1922, in rather exacting work (though the dosages were not specified) produced coma in rabbits with butyric acid and β-hydroxybutyric acid, though isobutyric acid and hydrochloric acid did not produce coma. He concluded that the cause of coma is a specific intoxication by acids related to butyric. Allen and Wishart[1], in 1923, were apparently the first to study this question more extensively when, by much more refined and better controlled methods, they attempted investigation of blood ketone levels. Using dogs and rabbits, and giving isotonic solutions in repeated dosage of all the

ketone bodies intravenously, they could produce changes progressing to coma and death almost invariably. Their conclusions were justly guarded and will be discussed later. Dungan[13] the following year did even more exacting work using normal and diabetic animals. By numerous analyses, he attempted to correlate the blood ketone levels with the apparent toxicity to injected ketone bodies. His results were variable and cannot be interpreted by a simple statement. His conclusions will be dealt with below, but it is evident that he was able to produce abnormalities in the experimental animal by ketone intoxication. Apparently the latest experimental work of this nature was performed by Schneider and Droller[36] in 1938. Using rabbits, they injected the ketone bodies at a constant rate and attempted to correlate the effects with the blood ketone concentration. They believed that they were able to produce coma invariably with "sufficient" doses of acetoacetic acid and its sodium salt, and concluded that this was the specific factor that caused the picture of diabetic coma in man. This work seems open to question; it has, in fact, been a major impetus for the writing of this paper.

3. Direct Evidence Opposing the Hypothesis of Primary Ketone Toxicity. It might seem apparent from the investigations cited that the ketone bodies may be highly toxic when injected into the experimental animal; however, there is conflicting evidence. Frerichs[16], in 1883, was one of the earliest to demonstrate the absence of potent toxicity in the ketone bodies. He gave 25 gm. of acetone per day for many days to dogs by mouth without effects, 20 gm. per day for many days of the ethyl ester of acetic acid and ethyl alcohol causing only mild lethargy, and 20 gm. of acetone per day for 5 days to humans in diabetic acidosis without apparent effect. Using acetoacetic acid, he gave 40 gm. by mouth without symptoms, and 25 gm. subcutaneously and intravenously as the salt and as the acid without apparent effect. Allen and Wishart[1] in their review mention the work of others. Albertoni, in 1884, gave 20 gm. of acetone by mouth to man without effect, though he was able to produce death in dogs using 8 gm. of acetone per kg. of body weight. Sternberg, in 1898, gave 5 gm. of β-hydroxybutyric acid by mouth to a woman daily for 5 days without causing symptoms, and 10 gm. for 2 days and 5 gm. for 3 days to a severe diabetic also without causing symptoms. Neubauer, in 1910, gave a diabetic human 30 gm. of l-β-hydroxybutyric acid without symptoms resulting. Dakin[10], in 1910, to a cat weighing 4 kg., gave 12 gm. of 8% sodium acetoacetate solution over a 6-hour period, and to a large dog, 12 gm. over a 4-hour period without fatality, though he does not give a definite statement regarding their appearance. Allen and Wishart[1], using isotonic solutions of β-hydroxybutyric acid and its neutral sodium salt in dogs, produced blood concentrations of total ketones of 11.8 and 20.9 mg. per 100 cc., expressed as acetone, causing very slight abnormalities followed by full recovery. More complete studies were done by Dungan[13] as a follow-up of this work. Using acetone, he attained a blood level of 280 mg. per 100 cc. which caused coma followed by full recovery. He did similar experiments with acetoacetic acid which gave delayed effects bearing no relation to the blood levels attained and producing in every case, severe hemolysis. One acetoacetic acid blood level was 142 mg. per 100 cc. expressed as acetone, yet the animal showed no abnormalities. Schneider and Droller[36], in 1938, using continuous intravenous infusions of acetone and sodium

acetoacetate, did not find changes in rabbits, irrespective of the amounts given, as long as the solutions were approximately isotonic with blood plasma. Most recently, Koehler *et al.*[25], in 1941, gave these substances intravenously to humans at the rate of 5 gm. per hour without observing any untoward symptoms. The blood total ketone levels reached were on the order of 20 to 26 mg. per 100 cc., expressed as acetone. There is, therefore, considerable evidence that the ketone bodies are not highly toxic substances in concentrations near those found in severe diabetic acidosis.

4. Indirect Evidence from Clinical Investigation. In contrast to animal experimentation, there is adequate confirmation almost without opposition regarding the biochemical changes in human diabetic acidosis and coma. But again, interpretation of these changes by different observers has resulted in controversial conclusions.

What is the correlation between the general clinical appearance of the patient in diabetic acidosis and his degree of acidosis and ketosis? Dungan[13] reviewed the literature to 1923. All figures of blood total ketone levels are expressed as acetone in mg. per 100 cc. Pre-coma and coma are clinical descriptive terms without regard to the changes in alkali reserve. Some discrepancies exist where observers use the term total acetone to mean acetoacetic acid and acetone but not β-hydroxybutyric acid. The reviewer has converted the figures below to the total ketone value to include β-hydroxybutyric acid. Seven cases of pre-coma were presented where the mean blood level was 97, with extremes of 38.5 and 205. Eleven cases of coma showed a mean level of 128, with extremes of 40.3 and 368.4. From Poulsen's review[33] we learn of other investigations.. Campbell, in 1922, described 3 cases of pre-coma with a mean blood ketone level of 64 and extremes of 49 and 82. Four cases of coma had a mean level of 108 with extremes of 79.5 and 121. Bucka, in 1926, described an early coma with a blood ketone level of 67, and 7 cases of coma with a mean level of 121, the extremes being 77 and 172. Møller presented 38 cases of coma, 10 of his own, the rest from the literature. Twenty-five cases ranged from 75 to 150, 7 from 25 to 75, and 2 from 150 to 200. Bertram[5], in 1932, presented 25 cases in full coma with an average blood ketone level of 133, and 36 cases in pre-coma with a mean of approximately 120. He was impressed by the similarity of the mean ketone level in these 2 groups. His highest value for coma was 254. Root[34], in 1945, studied 41 cases of diabetic ketosis. Unconsciousness did not occur at levels under 100 with one exception, that being at 68. His highest level was 195. The highest level noted without loss of consciousness was 162, and drowsiness was recorded in one case with a level of 46. Most recent is the work of Kety *et al.*[24], in 1948, who reported 8 cases of pre-coma with a mean blood ketone value of 66.3, and extremes of 38.5 and 90.6. Six cases of coma had a mean level of 98.4, with extremes of 47.7 and 154. Brügel[8] presented similar experiments. The highest level found was that presented by Falta[15] of work by Facskas reported as 565.

Several investigators have followed the blood ketone levels during therapy to note the correlation with the change in clinical condition and metabolic derangements. Dodds and Robertson[12], in 1930, studied 7 cases of severe diabetic acidosis and found no correlation of the blood ketone level or of the blood acetoacetic acid level with the clinical condition and recovery. Indeed, they noted a rise of acetoacetic acid level during early therapy

when the patient was much improved clinically. Poulsen[33] did similar studies on 4 severe diabetics. Examination of his data also shows no good correlation between clinical appearance and blood ketone levels during therapy. Martin[28] studied the relationship between the blood ketone levels and carbon dioxide combining power in diabetic acidosis. He noted that the correlation was not good. Bertram[5] made the interesting observation that there was a tendency to a greater depression of the serum freezing point in diabetic acidosis than in other diseases. He also did many follow-up studies of the blood ketone concentration during therapy and found poor correlation between time for recovery and loss of ketosis.

5. Opinions Regarding the Cause of Coma in Diabetic Acidosis. In order to compare the many conflicting opinions, they are grouped together according to the school of thought that they represent.

Acidosis Is the Primary Cause of Coma. Since the writings of Magnus-Levy[27] in 1911, no recorded conclusions were found where it was felt that acidosis is the direct and sole cause of the clinical picture of coma in diabetic acidosis. However, Peters and Van Slyke[32], in 1946, apparently lean heavily toward this opinion when they state that acidosis plus nonspecific factors leads to shock, coma and death. The investigations in denial of this opinion bear strong evidence that acidosis itself is not the most important feature, and most authors have voiced this opinion[14,21,29,36,42,44].

Hyperketonemia Is the Primary Cause of Coma. Binz[1], in 1886, is quoted as stating that the toxicity of β-hydroxybutyric acid is the cause of diabetic coma. Ehrmann *et al.*[14] concluded, in 1911, that in their own experiments butyric acid was the cause. It was Hurtley[21], in 1916, whose general conclusions were the first to carry real prestige: "The phenomena of diabetic coma are due to poisoning by aceto-acetic acid in the form of salts and not to a so-called acidosis". Tschun-Nien[42], in 1922, agreed with this but incriminated butyric and β-hydroxybutyric acids. Nóorden, in his book in 1907[29] made cautious statements, but by 1927[30] he readily stated that diabetic coma was due to a specific intoxication with one of the ketone bodies. Falta[15] made similar assertions. Schneider *et al.*[36], in 1938, from their own extensive experimentation in rabbits, concluded that acetoacetic acid was the toxic agent that caused the picture of diabetic coma. Barach[3], in a review in 1943, made the cautious statement: "When for one reason or another, ketone elimination lags and there is an excess of ketones in the blood and in the tissues, ketosis and intoxication follow, and the clinical picture of coma may sooner or later make its appearance". Finally, Joslin[23] in his most recent textbook states, "The clinical picture of diabetic coma . . . (is) attributable in a large part to the toxic effects of the ketone bodies".

Hyperketonemia Is Not the Primary Cause of Coma. Frerichs[16], in 1883, probably deserves credit for the first definite statements, resulting in part from his own experimental work. He concluded that neither acetone nor acetoacetic acid are toxic, and "diabetic coma cannot be attributed to them". Dungan[13], much later, stated that the ketone bodies played no direct part in the production of symptoms of diabetic coma in the majority of cases. Bertram[5] concluded from his experiments in 1932 that "ketone bodies cannot alone be made responsible for cerebral depression of diabetic coma" though he did not doubt that they had specific toxic actions. Brügel[8] states that Bertram leaned more heavily toward the importance of ketone specific toxic action, in publications of 1939. Baker[2],

in 1936, stated that the ketone bodies could not be indicted as the cause of acidosis in all cases of diabetic coma. From reviewing his paper, it seems fair to interpret his statements as subscribing to this group. Brügel[8], in 1941, concluded from his work that hyperketonemia can not be the decisive factor causing death in diabetic coma.

Acidosis Plus Specific Intoxication by the Ketone Bodies Are the Causes of Coma. Allen and Wishart[1] believed that symptoms of coma were due to the state of acidosis and to specific intoxication by the ketone bodies and that variations in the relative amounts of each might be responsible for the variations in the severity of the coma. Behre[4], in 1942, concurred when he stated, "It now appears probable that . . . ketosis is largely, if not entirely, responsible for the clinical picture of diabetic coma", but how much was due to acidosis from the ketone bodies and how much from specific intoxication by the ketone bodies, he said he did not know.

No Definite Conclusions. The majority of the recent writers must be classified under this heading. While it might appear from a cursory glance at parts of their communications that they should be classified as giving a definite opinion, complete and careful review of their papers often does not bear that out. This is mentioned in particular because of apparent misinterpretations that have been found in the literature reviews. Kety *et al.*[24], in 1948, stated that at least one of the ketone bodies is capable of producing coma and may act as a histotoxic agent; an equal possibility, they state, is that the blood ketone level is simply an index of less defined but more fundamental aberrations in the body. Many of the early investigators[2,5,6,20,21,31] believed that the ketone bodies might be important in coma production, yet they drew no specific conclusions as to the degree or manner in which they act. Within the last decade, Soskin[40], MacKay[26], Barach[3], Root[34], Brügel[8], and Best and Taylor[7] also recorded cautious and nonspecific conclusions, though they did not all lean toward the same trend of thought. Some suggest that the ketone bodies are entirely without harm; others do not doubt that ketone toxicity exists and plays a definite part in coma production, though they do not state that it is the primary cause or that it is by the specific toxic action of the ketone bodies.

Discussion. That great difference of opinion results from review of the same experimental evidence is quite reasonable when the number of variables are considered and compared. Definite differences in susceptibility of humans, rabbits, cats and dogs to formation of ketosis and to induced toxicity have been noted[5,13,21], though there is also evidence to the contrary[9]. Understandably, there is no good work of high ketonemia production in the human, and any inference from laboratory animals is certainly less than conclusive. Furthermore, it is possible that the diabetic human might react to ketosis differently from the nondiabetic, though here also the evidence is controversial[1].

Obviously, comparable doses given by different routes cannot be compared for relative toxicity. Thus, despite the great number of experiments performed to determine threshold levels for the toxicity of administered ketone bodies, insufficient administration under comparable conditions prevents one from making a good analysis of the data. It is quite evident that when 20 gm. of acetone or acetoacetic acid were given to an animal by stomach tube without the appearance of the odor of acetone on the breath or any detectable ketonuria[16], then sufficient amounts could not have

been absorbed. Therefore, unless the blood ketone level is known, the actual amount of drug given bears no definite significance.

Blood ketone body analysis is imperative if attempts are to be made to interpret resultant toxicity from ketone body administration in the experimental animal. It seems reasonable to believe that if the ketone bodies are themselves toxic, then some critical blood level, with great individual differences perhaps, should be found for the production of toxic symptoms. This has been studied by only a few previous investigators with generally insufficient data, though some conclusions are warranted.

It is easily understandable why so few studies have been done. There are numerous methods for quantitative ketone body analysis of the blood. It is a very time-consuming procedure that requires meticulous technique for accuracy. Blood ketone level determinations originating from different laboratories can be compared only roughly to each other. Bertram[5] found normal blood ketone values near 8.5 mg. per 100 cc., expressed as acetone. In our laboratory, we have not found normal values in excess of 3 mg. It is possible that a level of 368.4 mg. from Dungan's review[13] and that of 565 mg., expressed as acetone, by Facskas[15] might be measured as a fraction of that in another laboratory today. In addition, a confusion of terminology exists leading to misinterpretation of presented data. What substances are included in total acetone or total ketone bodies is not fully agreed upon.

The ketone bodies are very unstable substances. Solutions of them may contain toxic impurities. It is now generally agreed that in the blood stream acetone is a decomposition product of acetoacetic and β-hydroxybutyric acids and that the latter two are in equilibrium with each other. Similarly, great instability exists in the laboratory and great care must be taken in the preparation of acetoacetic acid so that it does not decompose and so that the agents used in its preparation are not left as contaminants of the final product. It is possible that many previous investigators, and particularly the early ones, were using rather weak solutions of acetoacetic acid or its sodium salt, possibly highly contaminated with ethyl alcohol and ethyl ether, both of which are powerful central nervous system depressants.

Probably the best refinements in experimental technique have been the attempts to have the rate and duration of administration as physiological as possible. Schneider and Droller[36] in particular discounted all previous work that was not done by infusions given at a constant rate. There is, nevertheless, no conclusive work in this regard, for it seems reasonable that the only true test would be to simulate a blood ketone level of diabetic ketosis in every possible respect, in particular by the maintenance of blood levels greater than 100 mg. per 100 cc., expressed as acetone, for a period of many days. Such an experiment has not yet been reported.

Much valuable information can be obtained from clinical observations, yet unjustified conclusions are easily made. That there is invariably a ketosis in diabetic acidosis seems certain. Baker[2], in 1936, reviewed 108 cases of diabetic acidosis and described several where no ketonuria was observed. He stated, "It is obvious that these patients have acidosis, yet there is no ketonuria or ketonemia, so that the ketone bodies cannot be indicted as the cause of acidosis in all cases of diabetic coma". This conclusion has been repeated by other reviewers[26] and specifically denied by some[8,37]. The differential diagnosis between

uremic acidosis, diabetic acidosis, alcoholic ketosis and acidosis[11], and perhaps others, is not always easy; so a mistaken diagnosis of diabetic acidosis must be considered if no ketosis is apparent. But more than this, diabetic acidosis and ketosis without ketonuria on any particular examination is not too rare a finding in the face of renal disease. Baker's conclusion that ketonemia did not exist because there was no ketonuria is not warranted, since no blood ketone analyses were done on any of these patients. Search through the literature has failed to uncover any case of true diabetic acidosis with proved absence of hyperketonemia.

Does hyperketonemia occur in states other than uncontrolled diabetes? It undoubtedly may occur whenever there is inadequate utilization of carbohydrate. In diabetes it is the lack of efficient utilization. In starvation it is the lack of sufficient available carbohydrate. Similarly, alcoholic excesses produce hypoglycemia because of the starvation that usually accompanies those conditions, aggravated by the inability of alcohol to be converted to glucose. Fever, exercise and hyperthyroidism create a relative carbohydrate insufficiency with ketosis resulting because of increased body demand. If this occurred in a magnitude comparable to that of diabetes, then the effects of hyperketonemia might easily be studied. Brügel[8] suggests that it does, and Schwenkenbecher[38] presented 2 cases where the blood ketone levels were 51 and 92 mg. per 100 cc. in non-diabetic patients who were vomiting. Other investigators[11] deny that these levels actually occur. Other maximum levels reported in the literature were between 20 and 25 mg. per 100 cc., expressed as total acetone. At any rate, severe hyperketonemia rarely, if ever, occurs in nondiabetic conditions.

In 1938, Schneider and Droller[36] concluded from their experimental work that "diabetic coma is due in the main to a specific intoxication by the acetoacetic anion". No more recent similar studies have been found in the literature. The conclusions of these investigators were surprising in view of the general disagreement up to that time. A careful inspection of this experiment was warranted. It was decided to attempt to duplicate their work. In general, they did all of their experiments on rabbits, using intravenous infusions at a constant rate and obtaining blood samples for quantitative ketone analysis at the onset of signs of severe abnormality in the animal. Such an experiment did indeed overcome many of the objections that could be made of previous work. In numerous experiments, they confirmed earlier reports warranting the conclusion that the acidosis was not the factor *per se* that caused coma, though it may potentiate the signs and symptoms.

Experiments were performed using 0.2, 0.3 and 0.5 normal acetoacetic acid infusing 60 to 155 cc. over an interval of 29 to 70 minutes. In every case, both coma and a decrease in the blood alkali reserve were noted. No abnormalities were apparent with infusions of 53 cc. of normal saline solution in 1 hour or with 22 cc. of isotonic acetone in 41 minutes. To obviate acidosis as a factor in this coma production, they prepared a neutral sodium salt of acetoacetic acid. To 4 rabbits, 0.143 or 0.154 normal sodium acetoacetate was given, 72 cc. to one very rapidly, and 110, 205 and 398 cc. in 1 hour to each of 3 others. No abnormal signs were produced; therefore blood ketone level determinations unfortunately were not done. It was concluded by them that they were unable to give "sufficient" sodium acetoacetate in this concentration to

cause abnormal signs. So they then used an 0.4 normal solution and produced coma in each of 5 rabbits, with quantities of 100 to 175 cc. over time intervals of 63 to 100 minutes. Blood ketone analyses on these rabbits all showed a hyperketonemia but without any correlation between the degree of hyperketonemia and the time of onset of coma.

An 0.145 normal sodium acetoacetate solution is isotonic with blood and 0.4 normal is about 2.8 times isotonic in concentration. Reducing their figures to grams administered per unit of time, they gave at a constant rate over a 1-hour period, 1.5, 3.0 and 5.9, and very rapidly, 0.9 gm. of isotonic sodium acetoacetate, causing no abnormalities in each of 4 rabbits. Using hypertonic solutions of sodium acetoacetate in 5 rabbits, they produced coma in every case giving the following amounts as calculated from their data: 4.6 gm. in 86 minutes, 6.7 gm. in 97 minutes, 5.4 gm. in 100 minutes, 4.0 gm. in 63 minutes, and 4.8 gm. in 64 minutes. Thus it is noted that 5.9 gm. in 1 hour produced no abnormalities when in isotonic solution, yet 4 rabbits developed coma with a smaller quantity in hypertonic solution, 2 reaching coma within a few minutes of 1 hour.

There is strong reason to suspect, therefore, that the hypertonicity of the solutions injected did in itself prove to be a toxic factor, irrespective of the agent injected, and that the results obtained may be artefacts of the concentrations of the solutions used, rather than the total dosage per unit of time of the specific agent used. This would tend to invalidate the definite conclusions drawn from these experiments regarding the toxicity of the ketone bodies.

Experimental Data. Methods. The following technique was used: The rabbit was weighed and then confined to a small box. An intravenous infusion by gravity drip was started into an ear vein. The rabbit was then moved to a larger box where it had freedom of motion. It was observed continuously throughout the experiment. All blood specimens for analysis were obtained by intracardiac puncture. Repeating the technique of Schneider and Droller, an end point of true coma was signified by the inability or apparent lack of attempt of the rabbit to right itself when placed on its side. This did not prove to be an easy end point, for several rabbits seemed definitely at this point, yet within a minute later seemed strong and active though there were no changes in the rate of infusion. Others seemed severely ill and went to death without ever passing through the state of coma described above.

Sodium acetoacetate was prepared as follows: 50 cc. of redistilled ethyl acetoacetate were hydrolyzed with 200 cc. of concentrated hydrochloric acid for 1½ hours at room temperature with constant, vigorous mechanical agitation. This solution was extracted 4 times with equal amounts of chilled ether. The ether extract was washed 3 times with 100 cc. of normal sodium bicarbonate, acidified with 2 normal hydrochloric acid to a pH of one, and reextracted twice with ether. The extract was vacuum distilled, leaving a yield of about 20 cc. of purified acetoacetic acid. This stock solution was placed immediately in an environment of −10° C., an aliquot first being removed for analysis in the Warburg apparatus. The strength of the stock acetoacetic acid varied from 1.2 to 3.05 moles per liter. Within 24 hours, sodium bicarbonate was added quantitatively to produce a solution approximately 0.15 normal with a pH near 7, and was used immediately. At the end of each experiment, the sodium acetoacetate was analyzed quantitatively for total ketone concentration.

Experimental Data. Results. Table 1 presents the results of infusion experiments performed on rabbits. Certain items are worthy of particular note. The volume of the solution injected apparently was not an important factor when isotonic with blood, for control rabbit number 1 tolerated 540 cc. of isotonic saline over a period of 175 minutes without any abnormal signs at any time and with continued good health for at least several weeks. This amount is probably well over 3 times the blood volume of that rabbit. Acetone was undoubtedly

toxic, though response varied greatly from animal to animal and did not correlate well with the blood ketone concentration. Two rabbits given isotonic and 1 hypotonic sodium acetoacetate showed no abnormalities. The total dosage was smaller than that used by Schneider and Droller, yet appreciable blood ketone levels were produced. One rabbit given 0.2 normal sodium acetoacetate was semi-stuporous throughout the entire infusion without progressing severity and with full recovery. It seems reasonable that this effect might be due to a contaminant, and it was known in advance that this solution did contain a small amount of ether. Four rabbits were given infusions of hypertonic saline comparable in concentration to the hypertonic sodium acetoacetate given by Schneider and Droller. The strength ranged from 2.1 to 2.3 gm. per 100 cc., approximately twice the isotonic concentration. Two rabbits died during the experiment, one was semicomatose at the completion of the experiment, and it died 5 hours later. The last was unsteady and sleepy at the end of the infusion and died 48 hours later.

From numerous blood ketone level determinations, it seems apparent that the blood ketone level became high within a few minutes after starting the infusion and increased only very little during the infusion. Thirty minutes after completion of the infusion, the blood ketone concentration was still near its maximal level.

Experimental Data. Conclusions. The following conclusions are made from these experiments: 1) Hyperketonemia can be produced in rabbits in the range found in diabetic acidosis in humans and maintained for several hours without apparent toxic effect upon the animal.

2) Hypertonic saline solution of about 3 times the tonicity of plasma can cause death in rabbits. Death is apparently the result of the hypertonicity itself, not of the volume of fluid injected, the rate of the infusion or the amount of sodium chloride given.

3) The toxicity noted in experiments performed by Schneider and Droller was apparently the result of or greatly influenced by the hypertonicity of the solution infused and not of the specific

TABLE 1.—THE EFFECT OF INTRAVENOUS INFUSIONS IN RABBITS

Rabbit No.	*Weight gm.*	*Solution infused*	*Quantity infused ml.*	*Average rate of infusion ml./min.*	*Duration of infusion min.*	*Blood total ketone concentration as acetone mg./100 ml.*	*Total dose gm.*	*Remarks*
1	1635	Saline, 0.85%	540	3.9	175		4.59	normal
2	1885	" 2.08%	485	3.0	161		10.19	coma at 161′, dead at 300′
3	1675	" 2.10%	280	3.3	85		5.88	coma at 78′, dead at 98′
4	1655	" 2.10%	325	2.6	125		6.83	coma at 134′, dead at 136′
5	1680	" 2.27%	420	2.1	205		8.82	stupor at 200′, dead at 48 hrs.
6	1680	Acetone, 0.3 M.	150	2.4	63	96.5 at 39′ 175.8 at 68′	2.61	stupor at 15′, coma at 64′, dead at 18 hrs.
7	1470	"	120	2.7	44	175.9 at 50′	2.09	coma at 44′, full recovery
8	1490	"	20	2.9	7	139.5 at 9′	0.35	dead at 71′, possible neck fracture
9	985	"	145	1.3	108	207.0 at 110′	2.52	lethargy at 110′, dead at 120′, death due to intracardiac puncture
10	1615	"	20	10.0	2	213.9 at 3′	0.35	dead at 2′
11	1540	"	150	1.5	98	129.2 at 100′	2.61	coma at 97′, full recovery
12	1440	"	160	1.2	128	135.0 at 130′	2.78	lethargy at 128′, full recovery
13	1385	Sodium acetoacetate, 0.043N.	200	2.7	75	37.8 at 77′	1.07	normal
14	1710	" 0.14 N.	130	1.9	70	56.8 at 70′	2.15	normal
15	1570	" 0.14 N.	150	1.8	85	63.0 at 85′	2.48	normal
16	1630	" 0.21 N.	160	2.0	79	77.4 at 79′	4.14	lethargic throughout, dead at 24 hrs; solution contaminated with ether?

The 3 substances that comprise the total ketones occur in the blood in diabetic ketosis in variable portions, acetone occupying the major portion. Concentrations noted above are comprised almost entirely of the solution infused. These levels thus represent quantities similar to or in excess of those found in the blood in human diabetic ketosis.

agent or quantity of the agent infused. This casts serious doubt on the validity of their conclusions.

Clinical Experimental Data. Forty-two patients with diabetic acidosis were studied at this hospital. Arterial blood specimens were obtained prior to therapy and were analyzed for total ketone content by the method of Greenberg and Lester[18]. An attempt is made to correlate the blood ketone concentration with the mental state. had a blood ketone level lower than the average for the group that was normal mentally. This probably does not represent a mistaken diagnosis, for this patient had an arterial blood carbon dioxide content of 6 vols. per 100 cc., a pH of 6.80, a glucose level of 630 mg., and a urea nitrogen of 20 mg. This case demonstrates also that the ketone bodies may not be the major factor in acidosis production, for this patient, with apparently normal

TABLE 2.—THE RELATIONSHIP BETWEEN MENTAL STATE AND BLOOD KETONE CONCENTRATION BEFORE THERAPY

Mental state	*No. of patients in group*	*Mean blood total ketone concentration, expressed as acetone, (mg./100 cc.)*	*Standard deviation*	*Range*	
				High	*Low*
1	11	60.1	26.9	123.0	34.9
2	13	73.4	24.4	111.8	25.8
3	7	85.0	35.6	117.0	21.0
4	11	109.8	37.4	154.0	47.7

In every case, the blood carbon dioxide content was less than 32 vols. per 100 cc. The mental state is described as follows: 1. normal; 2. lethargic, confused; 3. unconscious, responds to painful stimuli, reflexes intact; 4. unconscious, no response to painful stimuli, reflexes absent.

TABLE 3.—THE RELATIONSHIP BETWEEN MENTAL STATE AND BLOOD β-KETO ACID CONCENTRATION BEFORE THERAPY

Mental state	*No. of patients in group*	*Mean blood B-keto acid concentration, expressed as acetone, (mg./100 cc.)*	*Range*	
			High	*Low*
Conscious	5	19.8	27.3	7.6
Unconscious	7	31.3	41.7	17.2

Performed by the aniline citrite method in the Warburg apparatus.

Complete tabulation of the blood ketone levels, carbon dioxide and glucose content, and pH values for each patient will appear in a future publication. It is evident from inspection of Table 2 that, while there is a correlation of the mental state with the blood ketone levels on the average, there is great overlap. One patient with a normal mental state had a higher blood ketone concentration than the average of the group that was totally unresponsive, and higher than any single patient who was unconscious yet responsive to pain. One totally unconscious patient renal function and therefore reasonably good compensating ability, had a more severe acidosis than did some patients with 3 times the blood ketone concentration found here. Table 3 shows the relationship of the blood β-keto acid level to the mental state. Here again, while there is a correlation on the average of the mental state to blood β-keto acid concentration, the individual extremes are great.

Table 4 presents follow-up data during therapy of 14 patients in an attempt to correlate the changes in the individual of the mental state relative

to the blood ketone concentration. The trend of the blood ketone level changes is toward normal, as are all the metabolic abnormalities in the patients who recover. But this change does not correlate well in time relationship with the changes in clinical appearance. Patient A. M. appeared improved clinically as the blood ketone level rose, then later appeared less well as the degree of ketonemia decreased. Shortly before death, the patient lapsed again into unconsciousness, though the blood ketone level had dropped to 18.1 mg. At this time his arterial blood pH was 6.65, possibly the lowest to be reported in the literature. At autopsy, no disease other than the nonspecific changes of diabetes could be found. It is interesting

TABLE 4.—THE RELATIONSHIP BETWEEN MENTAL STATE AND BLOOD KETONE CONCENTRATION DURING THERAPY

Patient	*Interval after onset of therapy. (hrs.)*	*Mental state*	*Blood total ketone concentration, expressed as acetone. (mg./100 cc.)*
M. P.	0	1	123.0
	12	2	46.4
S. B.	0	1	48.9
	3½	1	29.8
D. L.	0	4	134.6
	3	3	107.0
A. B	0	4	85.5
	2	4	73.2
A. D.	0	4	71.4
	2	2	60.6
J. J.	0	1	38.5
	2	1	25.1
M. M.	0	2	88.8
	5	1	75.6
T. H.	0	2	90.6
	15	1	25.2
C. C.	0	2	42.7
	3	2	42.5
C. B.	0	2	83.5
	48	1	5.0
A. D.	0	2	82.0
	5	2	53.8
	20	1	12.1
A. R.	0	2	80.0
	3½	2	59.6
	8½	2	25.2
	18	2	2.8
H. R.	0	2	94.3
	3	2	77.0
	7	2	45.0
	12	2	39.0
	22½	1	24.0
A. M.	0	3	53.3
	3	2	72.0
	9	2	59.0
	22	2	19.0
	27	3	18.1

In every case, the blood carbon dioxide content was less than 32 vols. per 100 cc. Mental state is described as follows: 1. normal; 2. lethargic, confused; 3. unconscious, responds to painful stimuli, reflexes intact; 4. unconscious, no response to painful stimuli, reflexes absent.

to note that in this patient, 2000 units of insulin were given within the first 24 hours causing no improvement in his acidosis and no hypoglycemia, yet the blood ketone concentration showed a satisfactory return toward normal.

Summary. There is practically no disagreement that all of the ketone bodies can cause toxic effects if given in large enough doses, and some observers demonstrated specific effects on the respiratory and other brain centers. Furthermore, of the 3, acetoacetic acid is most toxic[1,5,12,13,21,36], β-hydroxybutyric acid is less toxic and is in equilibrium with acetoacetic acid, and acetone is a decomposition product with low toxicity. The question as to whether they are toxic in the concentration in which they appear in the blood in patients with diabetic acidosis is as yet unanswered. Though much direct experimental work has been done, the pitfalls are many, and it is not surprising that such a diversity of opinion exists. The ideal experiment has not yet been done in man or animals, the former being impossible with safety, the latter difficult. But to simulate the ketosis of uncontrolled diabetes, length of time may be an important factor. Acute versus chronic toxicity of many materials varies greatly. It is possible that a blood ketone level in animals of 100 mg. per 100 cc. may show no effects over a few hours, but, if it were maintained for a week or so, it might be highly toxic. It has been shown that the required critical blood levels of ether to produce coma in dogs decreases as the duration of administration increases[39]. The fact that ketosis is an absolutely constant finding in diabetic acidosis points naturally to a strong relationship between the two. Though individual response to drugs often varies greatly, if the ketone bodies are themselves the dominant factor in the production of the coma state, then some reasonable correlation should exist between the blood ketone level and the clinical state, as the blood ether level correlates with the clinical state[19]. All observers agree that the levels tend to be higher in coma than in pre-coma groups; but also, each observer has noted tremendous overlap. Of the 11 cases found in the literature where blood ketone levels were determined during therapy, there was poor correlation with the clinical condition. Although the general trend is of course back toward normal limits, it may be nothing more than one of the many derangements that returns to normal with treatment. Our findings in the 14 patients studied during therapy confirm the lack of good correlation. Even were there a good correlation, and even were there good evidence of ketone toxicity, the fact that a substance *can* be toxic does not mean in itself that it is the cause of a particular clinical syndrome.

Conclusions. 1. Acidosis *per se* does not seem to be the main cause of coma in diabetic acidosis, though it probably plays an important role in the production of symptoms.

2. It is highly unlikely that the ketone bodies are the primary cause of the clinical picture of coma. It seems more reasonable to view their presence as an indicator of metabolic derangements without particular toxicity in themselves, just as the blood urea is a nontoxic indicator of uremia.

3. It has been shown frequently that many factors must contribute to the clinical appearance and prognosis of the patient in diabetic acidosis. These probably include the degree and duration of acidosis and ketosis, the severity of the diabetes, the age and general health of the patient, the complications existing, the serum potassium concentration and others.

4. It is possible that there is a potent agent, as yet unknown, that may be the dominant factor in diabetic coma.

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COMBINED SALICYLATE AND PARA-AMINOBENZOIC ACID (Pabalate®) IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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FOR more than 75 years the salicylates have been the drugs of choice in the treatment of rheumatic diseases. Many mixtures and variations have been used in an effort to prevent toxic effects and prolong the period of effectiveness after administration. Although probably as much investigation has been directed at the possible mode of action of the salicylate drugs as any other agents, their use has been empirical, and their action generally attributed to antipyretic and analgesic effects.

In 1946, Dry *et al.*[2] described the synergistic action of para-aminobenzoic acid administered with sodium salicylate. With the same amount of salicylate as used in a patient previously, the addition of an equal amount of para-aminobenzoic acid increased the blood salicylate level 2 to 5 times. This was confirmed by Belisle[1] who advocated the use of this combination of drugs in the treatment of rheumatic fever. Rosenblum and Fraser[13] found that para-aminobenzoic acid (PABA) administered in rheumatic fever had a therapeutic activity of its own. Depression of fever and relief of joint pain were noted in 7 of their 9 cases after 2 days of administration of 1 to 3 gm. every 2 to 3 hours. The lack of toxicity of PABA even in large doses has been widely confirmed[14,15,16].

Another significant development in research on salicylates is their reported inhibitory effect on hyaluronidase. This enzyme, often referred to as the "spreading factor", is an important activator in the breakdown of the mucoid ground substance of connective tissue. Hyaluronic acid is apparently the principal constituent of this mucoid material, and is present in abundance in all the body tissues that become the seat of rheumatic disease[4]. It is, indeed, noteworthy that the basic pathological lesion of all the rheumatic, or collagen, diseases is focal degeneration in the interfibrillar substance of connective tissue. Meyer and Ragan[12] have also shown that the hyaluronic acid of the synovial fluid in rheumatoid arthritis is increased in amount but is partially hydrolyzed, indicating either imperfect polymerization of the polysaccharide or the presence of hyaluronidase. Euler and Ahlstrom[3] demonstrated that salicylates present in even low concentrations in the tissues inhibited the spreading effect of hyaluronidase. Guerra[4] substantiated this finding of the inhibitory action of salicylate on hyaluronidase by subcutaneous injection of hyaluronidase with a special dye into rabbits and human beings. Meyer[10] reported that Coss had confirmed the finding of a marked depression of hyaluronidase spreading effect

after administration of salicylate. He suggested, however, that this effect, as well as the beneficial action of salicylates on rheumatic manifestations might be in part an inhibition of hyaluronate production of mesenchymal cells. Meyer's[11] recently expressed idea of possible antigenic tissue specificity of hyaluronidase might explain in part the difference in principal site of attack of various rheumatic or collagen diseases (such as the heart in rheumatic fever, synovial membranes in rheumatoid arthritis, and blood vessel walls in periarteritis nodosa).

The inability to demonstrate free hyaluronidase in the blood or synovial fluids of patients with rheumatic diseases leaves us with the titer of antihyaluronidase in the serum as the nearest approach to an index of recent production of hyaluronidase in the tissues. In previous studies we[8] have demonstrated that streptococcal antihyaluronidase titers in rheumatoid arthritis were higher than in normal subjects or patients recently recovered from scarlet fever, but not as high as in patients with rheumatic fever or glomerulonephritis.

The purpose of the present study was to observe the effect of: *1*) salicylates, *2*) combined salicylates with para-aminobenzoic acid, and *3*) para-aminobenzoic acid alone on patients with rheumatoid arthritis, particularly concerning blood salicylate levels attained and the possible changes in the antihyaluronidase and antistreptolysin titers of the serum and synovial fluid of such patients, as well as for comparison of clinical efficacy as judged by relief of pain and stiffness, and ease of joint motion.

Method. Twenty-seven patients with active rheumatoid arthritis involving multiple joints with characteristic synovial swelling and elevated erythrocyte sedimentation rate were chosen for the study. In each case, the control salicylate level, antihyaluronidase titer and antistrepolysin titer were determined. The levels of antihyaluronidase titer were obtained by the mucin clot prevention method, but each was also checked by the turbidometric method. Antihyaluronidase and antistreptolysin titrations were done as described elsewhere[5,6,7].

The patient was then given 4 gm. (1 gm. 4 times daily) of sodium salicylate for at least 1 week, and the determinations were repeated. Clinical examination and questioning were carried out to compare this drug with previously used analgesics. Then, without the patient's knowledge, Pabalate, a combination of sodium salicylate and para-aminobenzoic acid*, was given in doses of 4 gm. each of salicylate and PABA daily. After at least 1 week of constant administration of this preparation, blood was again drawn, and the 3 determinations made. Clinical evaluation of effect was repeated at this point. After this period the patients were given 4 gm. daily of PABA alone for at least 1 week, and again the serum levels were determined and clinical evaluation performed. All 3 types of medication were made to appear identical with enteric coating. In 4 cases synovial fluids were aspirated and similar determinations made. Erythrocyte sedimentation rates were repeated at the time the blood samples were taken.

Results. The results are tabulated in Tables 1 and 2, where it is shown that in practically every case the administration of the sodium salicylate with PABA (Pabalate) resulted in a definitely higher salicylate level than with sodium salicylate alone in like amount.

Clinically, the patients had some relief from pain and stiffness when re-

* Kindly supplied by the A. H. Robbins Company.

ceiving salicylates or Pabalate but no similar effect resulted from the para-aminobenzoic acid alone. Nearly all of the patients remarked that none of these tablets gave more relief than aspirin. It was impossible for us to differentiate the analgesic or clinical effect of the Pabalate from that of the sodium salicylate alone. The effect of both on the sedimentation rate was slight. No rates were reduced more than a few millimeters throughout the study, and several were more rapid, even though the period of administration of Pabalate was of 4 to 6 weeks' duration in 12 of the patients.

There was no significant change in the antihyaluronidase titer or in the antistreptolysin titer throughout the periods of administration of the various combinations of drugs. The joint fluids were tested for the presence of free hyaluronidase. None could be demonstrated.

Seven of the patients could not tolerate sodium salicylate (even in enteric coated tablets) because of nausea. Seven patients could not tolerate the

TABLE 1.—EFFECT OF ADMINISTRATION OF SODIUM SALICYLATE AND PARAAMINOBENZOIC ACID, SEPARATELY AND IN COMBINATION, TO 23 PATIENTS WITH RHEUMATOID ARTHRITIS AS SHOWN BY BLOOD SALICYLATE LEVELS (IN GAMMA), ANTIHYALURONIDASE TITERS (A. H. T.), AND ANTISTREPTOLYSIN TITERS (A. S. T.)

			Control			*Sod. Salicylate (½ gm. daily)*			*Sod. Salicylate ½ gm. PABA (½ gm. daily)*			*PABA (½ gm. daily)*		
Init.	*Age*	*Sex*	*Sal.*	*A.H.T.*	*A.S.T.*	*Sal.*	*A.H.T.*	*A.S.T.*	*Sal.*	*A.H.T.*	*A.S.T.*	*Sal.*	*A.H.T.*	*A.S.T.*
G. M.	63	M	0	24	32	2.5	12	32	5.5	16	32	3.1*	12	32
E. B.	59	F	1.2*	192	24	3.6	128	24	8.1	192	24	0	192	24
E. R.	71	F	0	64	48	3.8	64	48	10	64	48	0.2	64	48
M. B.	78	M	0.4	48	48	4.2	4	48		nausea		0.6	(lost)	
R. T.	31	M	0.6	96	16	3.5	96	16	5.5	96	16	0	96	16
E. W.	32	F	0	48	16		nausea		5.0	24	16	0	24	16
E. B.	46	F	0	16	24	0.4	16	24	11.8	32	24	0	24	24
F. R.	60	M	0.4	24	12	0.6	24	12	1.5	24	16	0	12	16
H. G.	44	M	0	192	64	0.8	192	64	5.5	128	64	0	96	64
B. M.	23	F	0.4	24	32		nausea		0	12	48	0.5	12	32
T. H.	39	M	0	96	32	5.0	96	32	1.5	96	32	0	96	24
V. J.	57	F	0	192	64		nausea			nausea		0	256	64
L. P.	58	F	0	192	96	5.0	128	128	5.6	192	96	—	192	128
M. R.	36	M	0	192	48				4.0	128	48	0	128	48
H. B.	46	F	0	64	23	1.2	64	24		nausea			nausea	
A. C.	53	F	0.3	96	64		nausea		2.8	128	64	0.2	96	64
G. M.	41	F	0	48	24		nausea			nausea			nausea	
C. M.	55	F	0	(lost)		2.0	128	48		nausea		0	96	48
A. M.	53	F	0.6	128	64	1.6	192	64		nausea		0	192	64
M. R	70	F	0	48	48	4.0	32	48	5.2	48	48		(lost)	
E. H.	59	M	0	48	16	6.2	48	16	4.6	48	16	—	—	—
J. J.	63	M	0.6	16	16	—	—	—	4.4	16	—	0	16	16
E. U.	53	F	0.2	384	64	1.8	384	64		nausea		0	384	64

* Had taken aspirin.

TABLE 2.—EFFECT OF ADMINISTRATION OF PABA AND SALICYLATE, SEPARATELY AND IN COMBINATION, ON BLOOD AND SYNOVIAL FLUID** SALICYLATE LEVELS, A. S. T. AND A. H. T. IN 4 CASES OF RHEUMATOID ARTHRITIS

			Control			*Sod. Salicylate (½ gm. daily)*			*Sod. Salicylate ½ gm. (PABA ½ gm. daily)*			*PABA (½ gm. daily)*		
Init.	*Age*	*Sex*	*Sal*	*A.H.T.*	*A.S.T.*	*Sal*	*A.H.T.*	*A.S.T.*	*Sal*	*A.H.T.*	*A.S.T.*	*Sal.*	*A.H.T.*	*A.S.T.*
W. M.	31	M	0	128	24	1.0	192	24	4.0	192	24	0	128	24
W. M.*	31	M	0	192	—	0.5	96	16	2.0	192	—	—	—	—
F. S.	24	F	0.2	48	64	1.5	12	96	10	12	128	0	24	64
F. S.*	24	F	0	16	—	—	—	—	2.2	16	—	—	—	—
L. R.*	57	M	0.2	12	—	0	12	24	—	—	—	—	—	—
L. R.	57	M	0.4	16	24	4.2	16	24	4.4	12	24	0	12	32
H. H.	49	F	0	32	24		nausea		4.4	16	—	0	16	16
H. H.*	49	F	0	16	—	—	—	—	2.4	16	—	—	—	—

* Joint fluid.
** No free hyaluronidase could be detected in serum or synovial fluid.

Pabalate because of nausea, and 2 patients could not even tolerate PABA tablets. In all these cases the nausea did not appear until a day or two after the beginning of this therapy.

Discussion. The reason for the development of nausea in the patients who apparently could not tolerate the sodium salicylate alone or in combination with PABA is somewhat obscure. Since the symptoms appeared after administration of the drugs for a day or more it seems likely that they are produced by some general reaction after absorption rather than by local irritation of the stomach[9]. The enteric coated tablets have not prevented this complication. Why 2 patients could not tolerate even the PABA alone is even more obscure, but the identical appearance of the tablets with those that previously nauseated them suggests a purely psychic factor.

The mere raising of the blood salicylate level in rheumatoid arthritis does not seem to be of particular significance in producing greater relief from pain, as no clear correlation between the degree of relief and salicylate level could be noted. Since the effect of the salicylate and PABA on the antihyaluronidase titer was negligible, this method of study cannot be utilized to confirm previously reported antihyaluronidase effects from salicylate administration. In no case was the erythrocyte sedimentation rate reduced more than a few millimeters from the control rate, even on administration of Pabalate® for periods up to 6 weeks, so the drug apparently has no "specific" antiarthritic effect.

Conclusions. 1. Experiments on 27 patients with rheumatoid arthritis confirm earlier observations by others that the administration of a combination of sodium salicylate with para-aminobenzoic acid produces a higher blood salicylate level than with an equal amount of salicylate used alone.

2. No change in the antihyaluronidase titer could be detected from the administration of salicylates alone or in combination with para-aminobenzoic acid.

3. From a clinical standpoint, the combination of salicylate and para-aminobenzoic acid seems to hold little advantage over salicylates alone in the treatment of rheumatoid arthritis.

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CORRELATION OF ERYTHROCYTE SEDIMENTATION RATES AS DETERMINED BY THE ROURKE-ERNSTENE AND BY THE WINTROBE-LANDSBERG METHODS*

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[From the House of the Good Samaritan (Children's Medical Center)]

Different methods of measuring the erythrocyte sedimentation rate are widely employed not only in closely associated hospitals but often even within the same hospital. Although all methods are based on the settling rate of erythrocytes from plasma in anticoagulated blood, the size of the tubes, anticoagulants used, and units of measurement differ widely among the various methods. Furthermore, some methods correct for the influence of the total number of red blood cells or the packed red cell volume on the sedimentation rate; while other methods make no such correction. Hence, these variations in technique make correlation of absolute values of one method with another a confusing and difficult problem. This difficulty in interpreting corrected rates of sedimentation in terms of elevation or normalcy *per se* or in relation to prior or subsequent values obtained by various methods arises frequently in the care of rheumatic fever patients, and of necessity is resolved largely by the experience and judgment of the individual physician.

Studies correlating sedimentation rate determinations by various methods have been done. The Cutler, Linzenmeier, and Westergren methods were found by Greisheimer[2] to yield sedimentation measurements which clearly were "in part, specific for the technique employed." McKinley[6] has demonstrated a coefficient of correlation of 0.77 between results obtained by the Westergren macromethod and the Kato micromethod. The methods of Linzenmeier, Westergren, Cutler, Wintrobe-Landsberg, and Rourke-Ernstene were compared by Ham[3] on the basis of the degree of fibrinogen-sedimentation correlation for each technique and the accuracy of estimating fibrinogen from the sedimentation rate under similar experimental conditions. The correlation of the Rourke-Ernstene corrected sedimentation index with fibrinogen was found to be linear; while the Wintrobe-Landsberg corrected rate correlation was described as roughly linear up to 400 mg. of plasma fibrinogen and over this level disproportionately slow.

* This study was supported by a grant from the Helen Hay Whitney Foundation.

The Wintrobe-Landsberg and the Rourke-Ernstene, the latter often slightly modified, are commonly used methods of measuring the erythrocyte sedimentation rate. Each of these techniques employs the same sedimentation tube, often the same anticoagulant, and both correct for cell volume. Use of the same tube and anticoagulant made possible in a large series simultaneous sedimentation rate measurements by both the Wintrobe-Landsberg and the Rourke-Ernstene methods on the same sample of blood. The purpose of this

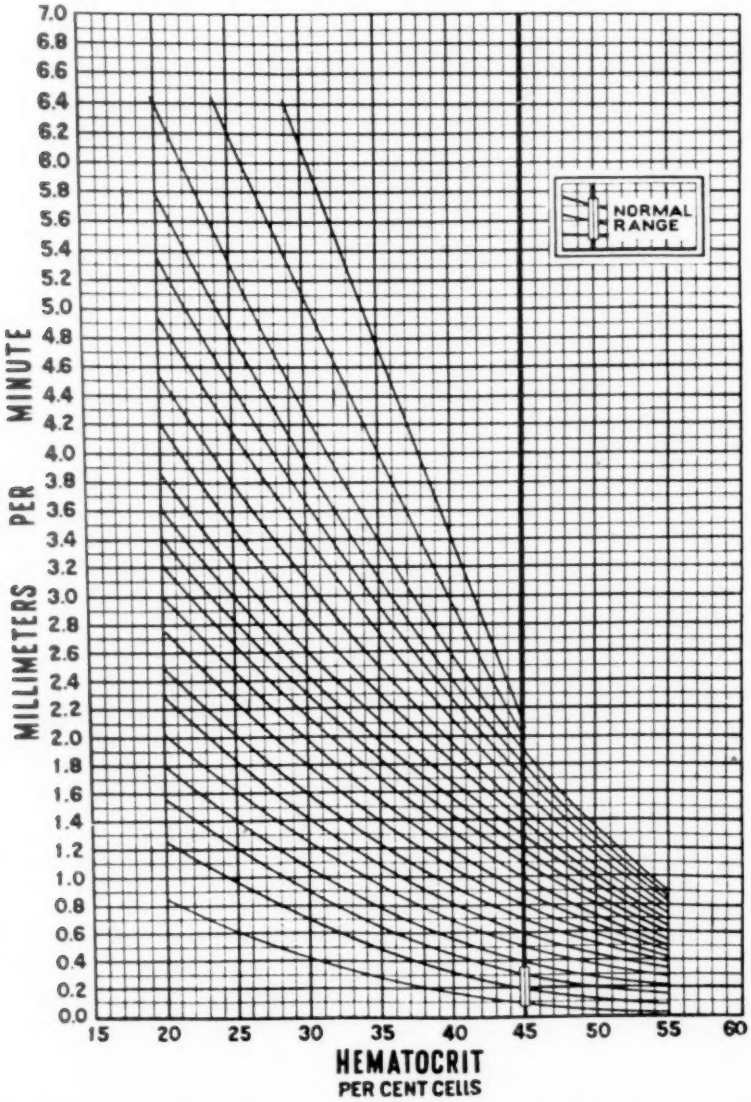

FIG. 1.—Rourke-Ernstene Hematocrit Correction Chart. The sedimentation rate is recorded in mm. per minute. (Reproduced from the original article[7] with permission of authors and publisher.)

report is: first, to compare the absolute values of the overall range and the established limits of normal for the Wintrobe-Landsberg and modified Rourke-Ernstene methods; second, to compare their respective hematocrit correction charts; and, third, to prepare a graph for the conversion of values of one method into terms of the other.

Material Studied and Methods. The present report is based on the study of 2709 bloods routinely drawn by venous puncture at the House of the Good Samaritan. The erythrocyte sedimentation rate was determined both by the Wintrobe-Landsberg and modified Rourke-Ernstene methods on each pipette into the standard Wintrobe tube, used both for measurement of the rate of settling of the red blood cells and for hematocrit. Readings to the half millimeter in accuracy were recorded every 5 minutes for 1 hour, and the rate of fall in mm. per minute was determined for the most rapid 10-minute-period of fall. The sedimentation tubes were then spun for 30 minutes at 3000 r.p.m. and the hematocrit readings then made. The corrected sedimentation index was finally determined, using the Rourke-Ernstene correction chart[1,5,7]. This chart is reproduced in Fig. 1.

The corrected sedimentation index by the Wintrobe-Landsberg method was arrived at on the same blood and by the same technical procedure, except that only the total fall

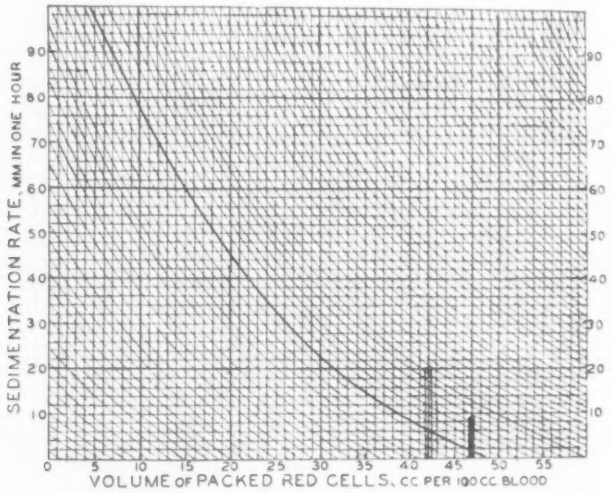

FIG. 2.—Wintrobe-Landsberg Hematocrit Correction Chart. (Reproduced from the original article[8] with permission of the authors.)

of these. The technique used by us was as follows: Venous blood was collected in a clean dry syringe without venous stasis. Three cubic centimeters of the blood were immediately transferred to a test tube containing the oxalate mixture described by Heller and Paul[4] and advocated by Ham[3]. The tubes were prepared by drying in an oven after introduction of 1 cc. of solution made up on 6 gm. of crystalline potassium oxalate and 9 gm. of crystalline ammonium oxalate dissolved in 2500 cc. of distilled water. Within 3 hours after the collection, the blood was well mixed by tipping and was then introduced by a clean dry capillary in 1 hour was recorded and the Wintrobe-Landsberg hematocrit correction chart[8] was used. This chart is reproduced in Fig. 2.

Results. A comparative study was made of the uncorrected sedimentation indices of the 2709 pairs of determinations by the 2 methods. Space does not permit publication of every one of the pairs of indices. Therefore, the results have been condensed into 12 groups and are presented in Table 1. The range for the Rourke-Ernstene in-

dices is 0.00 to 2.00 mm. per minute, and the range for the Wintrobe-Landsberg indices is 0.0 to 59.1 mm. per hour. From the original data the medians and the 95 percentile ranges have been computed for each of the 12 groups and are shown in Tables 2 and 3. In Table 2 the uncorrected Rourke-Ernstene indices are used as the basis of comparison; while in Table 3 the uncorrected Wintrobe-Landsberg indices are used as the basis of com-

TABLE 1.—CORRELATION OF 2,709 PAIRS OF UNCORRECTED SEDIMENTATION INDICES

Rourke-Ernstene Sedimentation Rate Indices
mm. per min.

Wintrobe-Landsberg Indices mm. per hour	*0.00 to 0.10*	*0.11 to 0.20*	*0.21 to 0.30*	*0.31 to 0.40*	*0.41 to 0.50*	*0.51 to 0.60*	*0.61 to 0.70*	*0.71 to 0.80*	*0.81 to 1.00*	*1.01 to 1.25*	*1.26 to 1.50*	*1.51 to 2.00*
0.0 to 5.0	150	53										
5.1 to 10.0		278	86	2								
10.1 to 15.0		5	266	161	16	1						
15.1 to 20.0			3	172	205	33	3		1			
20.1 to 25.0				7	131	158	56	7				
25.1 to 30.0					3	69	143	77	12		1	
30.1 to 35.0						1	55	89	52	4	1	2
35.1 to 40.0							3	28	73	31	3	7
40.1 to 45.0								1	21	67	20	15
45.1 to 50.0										41	24	34
50.1 to 55.0											9	25
55.1 to 60.0												4

The figures in the blocks represent the number of determinations.

parison. The median and percentile ranges were preferred as a basis of comparison to the mean and standard deviation because of marked skewing of the distribution curves in the selected categories. Data of Tables 2 and 3 are graphically presented in Fig. 3, the data of Table 2 being represented by solid lines and of Table 3 by the broken lines. The graphs were prepared by plotting for one method the medians and the range within which 95% of the tests fall against the corresponding mid point of each of the 12 groups of the other method. Fig. 3 clearly demonstrates the agreement of uncorrected sedimentation indices obtained by each method. In spite of the lack of linearity, the coefficient of correlation between these two methods was 0.94.

TABLE 2.—COMPARISON OF UNCORRECTED SEDIMENTATION INDICES BY ROURKE-ERNSTENE AND WINTROBE-LANDSBERG METHODS, USING THE ROURKE-ERNSTENE METHOD AS THE BASIS OF COMPARISON

Rourke-Ernstene Range mm./minute	*Corresponding Indices by Wintrobe-Landsberg Method*			
	Median mm./hour	*95% Range*		*Number of cases*
		mm./hour	*mm./hour*	
.00 to .10	2.2	4.3	2	150
.11 to .20	6.7	10.0	3.9	336
.21 to .30	11.4	14.8	8.1	355
.31 to .40	15.3	19.9	11.0	342
.41 to .50	19.3	24.3	14.1	355
.51 to .60	23.2	28.5	17.3	262
.61 to .70	27.4	34.2	21.0	260
.71 to .80	31.0	38.1	24.4	202
.81 to 1.00	35.9	42.6	27.1	159
1.01 to 1.25	43.4	48.6	34.7	143
1.26 to 1.50	46.3	51.6	31.6	58
1.51 to 2.00	48.2	56.9	35.3	87

TABLE 3.—COMPARISON OF UNCORRECTED SEDIMENTATION INDICES BY ROURKE-ERNSTENE AND WINTROBE-LANDSBERG METHODS, USING THE WINTROBE-LANDSBERG METHOD AS THE BASIS OF COMPARISON

Wintrobe Range mm./hour	*Corresponding Indices by Rourke-Ernstene Method*			
	Median mm./min.	*95% Range*		*Number of cases*
		mm./min.	*mm./min.*	
0 to 5.0	.07	.20	.00	203
5.1 to 9.0	.17	.39	.11	282
9.1 to 14.0	.27	.41	.14	448
14.1 to 17.0	.37	.51	.24	248
17.1 to 20.0	.45	.61	.32	347
20.1 to 26.0	.56	.74	.42	324
26.1 to 29.0	.67	.89	.52	192
29.1 to 33.0	.74	1.18	.63	196
33.1 to 40.0	.88	1.64	.64	208
40.1 to 45.0	1.16	1.90	.83	124
45.1 to 50.0	1.35	1.97	1.02	99
50.1 to 55.0	1.67	1.99	1.28	34

Inspection of Fig. 3 indicates that the medians are almost superimposable. Because of this high correlation and similarity a single curve is presented in Fig. 4 so that it may be used in a practical manner for converting results of one method to that of the

other. The 95 percentile ranges have been similarly united in Fig. 4; the curves have been smoothed graphically.

In view of the high correlation of the overall range of sedimentation rates of the 2 methods, it was of interest to study the relationship of the established normal values for each method. Since the sedimentation rate is affected by the blood cell volume, both the Rourke-Ernstene and the Wintrobe-Landsberg techniques involve a correction based on an arbitrary normal hematocrit. The established normals have been corrected to these hematocrits. The Rourke-Ernstene technique, for which the upper limit of normal corrected sedimentation index is 0.40 mm. per minute* for both males and females, corrects all sedimentation rates to a hematocrit of 45%.

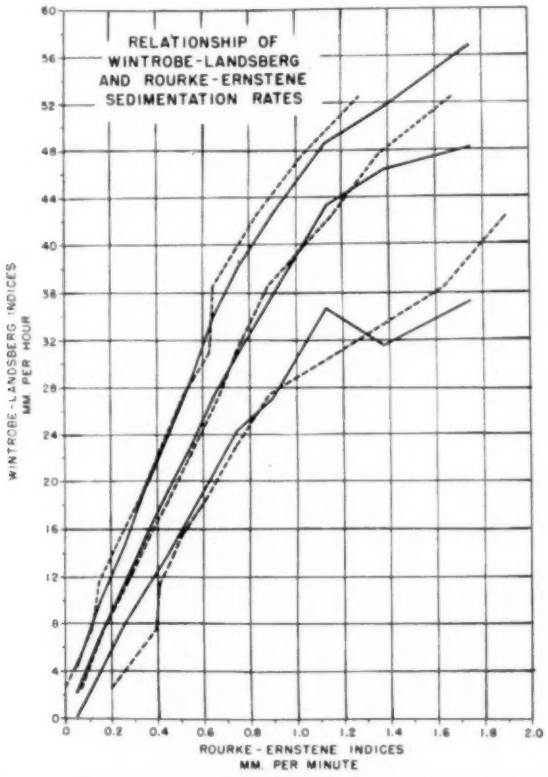

FIG. 3.—Correlation of sedimentation indices by Wintrobe-Landsberg and Rourke-Ernstene methods. Medians and 95 percentile ranges above and below the medians are indicated. The solid lines represent the relationship when Rourke-Ernstene indices were used as basis of comparison. The interrupted lines represent the relationship when Wintrobe-Landsberg indices were used as basis of comparison.

The Wintrobe-Landsberg method corrects to an arbitrary normal hematocrit of 47% for men and 42% for women. The Wintrobe-Landsberg established

* Rourke and Ernstene use 0.38 mm. per minute as the upper limit of normal for the corrected sedimentation index. At the House of the Good Samaritan, it has been customary to use 0.40 mm. per minute as upper limit of normal.

upper limits for normal corrected sedimentation indices are 20.0 mm. per hour for females, and 9.0 mm. per hour for males.

For valid comparison of the normal ranges of corrected indices for each method, it is obvious that different "normal" hematocrits cannot be used. Therefore, we have arbitrarily chosen 45% as the "normal" hematocrit. With this figure the upper limit of normal for the corrected sedimentation index remains 0.40 mm. per minute for the Rourke-Ernstene method. When the figure 45% for the normal hematocrit is applied to the Wintrobe-Landsberg correction chart, the upper limit of normal for females is changed from 20.0 mm. per hour to 16.0 mm. per hour, and for males from 9.0 mm. per hour to 12.0 mm. per hour.

Attention should be called to the fact that Wintrobe and Landsberg believed that normal males have a somewhat slower sedimentation rate than normal females; whereas Rourke and Ernstene found no such difference between the sexes. It is evident from Fig. 4 that the Wintrobe-Landsberg upper limit of normal for females (16 mm. per hour on basis of 45% hematocrit) is practically indentical with the Rourke-Ernstene upper limit of normal for males and females (0.40 mm. per minute on the basis of a 45% hematocrit). If the Wintrobe-Landsberg upper limit of

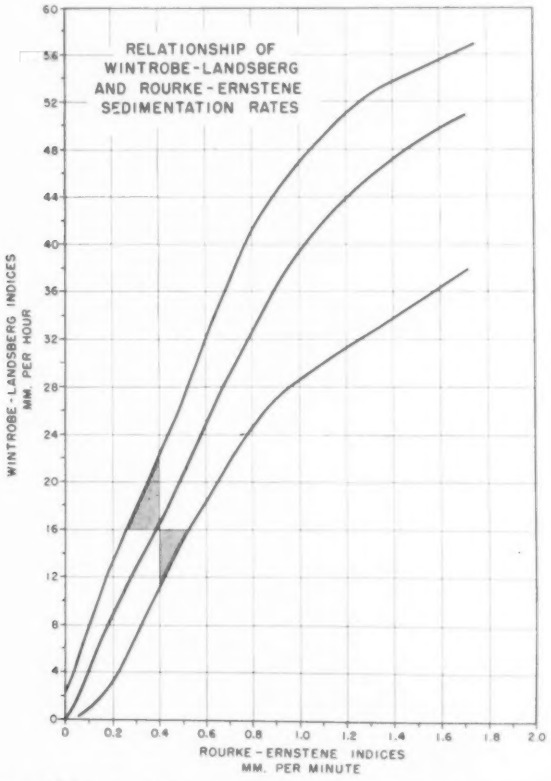

FIG. 4.—A chart obtained by combining the data of Fig. 3 and constructed for the practical purpose of converting sedimentation rates of one method into terms of the other method. The median and 95 percentile range above and below the median are indicated.

normal for males is converted by Fig. 4 to the Rourke-Ernstene index, it is found that the corresponding upper limit for the Rourke-Ernstene method would be only 0.28 mm. per minute. Obviously certain sedimentation indices for males which would be considered to be normal by Rourke and Ernstene would be classified as abnormally rapid by Wintrobe and Landsberg. Our data do not indicate which interpretation is correct, but for purposes of comparison we have arbitrarily chosen 0.40 mm. per minute for the Rourke-Ernstene and 16.0 mm. per hour by the Wintrobe-Landsberg method as the upper limits of normal for both sexes.

TABLE 4.—COMPARISON OF THE ROURKE-ERNSTENE AND WINTROBE-LANDSBERG METHOD WITH RESPECT TO NORMALITY

Wintrobe-Landsberg Method (mm./hr.)	*Rourke-Ernstene Method*: *Less than 0.40 mm./min.*	*More than 0.40 mm./min.*	*Total number of cases*
Less than 16.0	1055	37	1092
More than 16.0	128	1489	1617
Total number of cases	1183	1526	2709

Using these figures for upper limits of normal, we have determined the number of tests normal by one method which would be abnormal by the other, and the number of tests abnormal by one method which would be normal by the other. These data are presented in Table 4. It is evident that of a total of 1183 tests which were normal by the Rourke-Ernstene method (less than 0.40 mm. per minute) only 128 (10.8%) were abnormally rapid by the Wintrobe-Landsberg method (above 16.0 mm. per hour). Furthermore, of a total 1526 tests which were abnormally rapid by the Rourke-Ernstene method (above 0.40 mm. per minute) only 37 or 2.4% were within normal limits by the Wintrobe-Landsberg method (less than 16 mm. per hour).

Of more practical importance in connection with the problem of converting from one method to the other is the fact, evident from Fig. 4, that a Wintrobe-Landsberg index of above 22 mm. per hour would be also abnormally rapid (above 0.40 mm. per minute) by the Rourke-Ernstene method. Wintrobe-Landsberg indices of 11.0 mm. per hour or less will ordinarily be normal (less than 0.40 mm. per minute) by the Rourke-Ernstene method.

If the comparison is made in the reverse order, it is evident that a sedimentation rate above 0.52 mm. per minute by the Rourke-Ernstene method would practically always be above the upper limit of normal (16.0 mm. per hour) by the Wintrobe-Landsberg method. Sedimentation indices of less than 0.26 mm. per minute by the Rourke-Ernstene method would almost invariably be normal (less than 16.0 mm. per hour) by the Wintrobe-Landsberg method.

In Fig. 4 the shaded area represents the range in which the indices of the two different methods may disagree in respect to normality. All indices below the shaded areas will be normal by both methods, and all indices above the shaded area will be abnormally rapid by both methods.

Finally an attempt has been made to determine whether a close correlation still holds when uncorrected indices by each of the two methods are corrected for variations in hematocrit, the correction for the Wintrobe-Landsberg indices being made from the correction chart of Wintrobe and Landsberg and the correction for the Rourke-Ernstene indices being made from the correction chart of Rourke and Ernstene. In effect this is a test of the similarity of the two different correction charts. For this study, the data of which are shown in Table 5, the following procedure has been followed:

A series of Rourke-Ernstene uncorrected indices covering the range 0.10 to 1.30 mm. per minute were arbitrarily chosen. These are recorded in column 1. The arbitrary hematocrits 35, 38, 40 and 43% were chosen and these are recorded in column 3. The indices in column 1 were corrected for the various hematocrits by Rourke-Ernstene correction chart, and these corrected indices are recorded in column 4. From the median curve in Fig. 4 the uncorrected Wintrobe indices corresponding to the various uncorrected Rourke-Ernstene indices of column 1 were determined, and these are recorded in column 2. The indices of column 2 were corrected for the various hematocrits by the Wintrobe-Landsberg correction chart, and these corrected indices are recorded in column 6. From the median curve of Fig. 4 the Wintrobe-Landsberg indices corresponding to the various corrected Rourke-Ernstene indices of column 4 were determined, and these are recorded in column 7. In similar

TABLE 5.—COMPARISON OF HEMATOCRIT CORRECTIONS BY THE ROURKE-ERNSTENE AND WINTROBE-LANDSBERG METHODS

Uncorrected indices from Fig. 4				*Corrected W-L converted to R-E*		*Corrected R-E converted to W-L*
R-E mm./min.	*W-L mm./hr.*	*Hematocrit %*	*Corrected R-E mm./min.*	*mm./min.*	*Corrected W-L mm./hr.*	*mm./hr.*
.1	4.2	35	.0	.0	.0	.0
.3	12.8	35	.10	.04	1.5	4.2
.5	20.6	35	.20	.17	7.6	8.6
.7	28.8	35	.34	.34	14.3	14.4
.9	36.2	35	.48	.48	20.0	19.8
1.1	41.6	35	.60	.59	24.5	24.8
1.3	45.6	35	.74	.67	27.6	30.2
.1	4.2	38	.0	.0	.0	.0
.3	12.8	38	.15	.11	4.8	6.6
.5	20.6	38	.28	.27	11.5	12.0
.7	28.8	38	.44	.45	18.5	18.2
.9	36.2	38	.59	.60	25.0	24.4
1.1	41.6	38	.73	.72	29.4	30.0
1.3	46.6	38	.88	.80	32.5	35.4
.1	4.2	40	.04	.0	.0	1.4
.3	12.8	40	.18	.16	7.0	7.8
.5	20.6	40	.34	.34	14.3	14.3
.7	28.8	40	.51	.51	21.0	21.0
.9	36.2	40	.67	.68	28.3	27.7
1.1	41.6	40	.82	.80	32.5	33.2
1.3	46.6	40	.98	.90	36.0	38.6
.1	4.2	43	.07	.06	2.0	2.6
.3	12.8	43	.25	.25	10.8	10.8
.5	20.6	43	.43	.42	17.5	17.8
.7	28.8	43	.62	.62	25.5	25.6
.9	36.2	43	.80	.81	33.0	32.5
1.1	41.6	43	.98	.96	38.0	38.6
1.3	46.6	43	1.17	1.09	41.5	43.0
(Col. 1)	(Col. 2)	(Col. 3)	(Col. 4)	(Col. 5)	(Col. 6)	(Col. 7)

fashion from the median curve of Fig. 4, the Rourke-Ernstene indices corresponding to the corrected Wintrobe-Landsberg indices of column 6 were determined, and these are recorded in column 5.

The similarity of the corresponding figures in columns 4 and 5 and of the corresponding figures in 6 and 7 is apparent. This similarity in turn indicates close agreement in the hematocrit corrections obtained by the Wintrobe-Landsberg chart and by the Rourke-Ernstene chart.

Conclusions. 1) The erythrocyte sedimentation rate was determined by both the Wintrobe-Landsberg and Rourke-Ernstene methods on each of 2709 blood samples, and the results obtained by one method were correlated with those obtained by the other.

2) The coefficient of correlation of these two different methods was found to be 0.94.

3) Of a total of 1183 tests which were normal by the Rourke-Ernstene method 128 (10.8%) were abnormally rapid by the Wintrobe-Landsberg method, and of 1526 tests which were abnormally rapid by the Rourke-Ernstene method, 37 (2.4%) were within normal limits by the Wintrobe-Landsberg method.

4) The hematocrit correction chart used in the Wintrobe-Landsberg method was found to give results very similar to that obtained by the Rourke-Ernstene correction chart.

5) A chart has been constructed which shows the relationship of the sedimentation rates obtained by the two different methods. This chart may be useful for converting the results of one method into terms of the other. The range in which indices normal by one method overlap with indices abnormal by the other is indicated.

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RELATION OF SODIUM CHLORIDE DEPLETION TO URINE EXCRETION AND WATER INTOXICATION*

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The metabolism of sodium chloride has received considerable attention in the clinical literature in recent years. Evidence has been obtained to show the beneficial effects of diets low in sodium chloride in the treatment of cardiac failure[7] and certain cases of hypertension[3,5]. However, the possibility that diets low in sodium chloride may produce untoward effects has received little attention. Schroeder[10] reported a condition which he refers to as the "low salt syndrome" in which there occurred renal failure secondary to low serum sodium concentration. This syndrome was observed in patients in cardiac failure who were receiving mercurial diuretics. Low serum sodium levels were noted in cases of nephrosis with edema. The administration of parenteral hypertonic sodium lactate to such patients produced a diuresis and decrease of edema[2]. McGuire[6] also found elevated blood urea and creatinine levels in patients with a low serum sodium which were reversed by the administration of salt.

It is evident, then, that if serum sodium falls to too low a level it may interfere with renal function. Although all of the above papers point out that a severe restriction of dietary sodium may affect renal function, no experimental studies have been reported. The present report ascertained some of the effects of sodium depletion in 2 species of experimental animals. Studies on urine excretion during water tolerance tests were performed in both the normal and salt depleted dog and rat. Observations were also made on the relationship of sodium chloride depletion to the development of water intoxication as evidenced by anorexia, apathy, irritability and convulsions.

Methods. Albino rats (200 to 300 gm.) and adult mongrel dogs were used in this study. Sodium depletion was accomplished by glucose injection[1]. In this technique intraperitoneal glucose is administered. As the glucose is absorbed a certain amount of sodium chloride will cross the peritoneum and be present in the peritoneal solution. At a maximum time interval a paracentesis can be performed removing glucose together with a large amount of sodium chloride. The dogs received intraperitoneally 5% glucose, 100 cc. per kg. of body weight. All the intraperitoneal fluid was removed 5 hours later by paracentesis under pentothal anesthesia. In most of the cases the same volume of fluid was recovered that had been originally injected. The rats received intraperitoneally 30 cc. of 5% glucose. The intraperitoneal fluid was removed by paracentesis 3 hours later under ether anesthesia.

Following the paracentesis, the dogs and rats were placed on a low sodium diet† and allowed to equilibrate before being hydrated. Hydration studies in dogs were performed only after the serum sodium levels had stabilized. No studies were done on the rats for 4 days, the first hydrations being performed routinely on the 5th day after paracentesis.

†Diet: Casein	19.75%
Lard	21.22%
Sucrose	55.20%
Bone Ash	2.56%
Potassium Phosphate	0.16%
Yeast Extract	0.49%
Mag Sulfate	0.16%
Fe Am Citrate	0.23%
Ca Lactate and Phosphate	0.23%
Oleum Percomorphum	10 drops/½ g.

* This study was aided by a grant from Parke, Davis & Co.

The last 2 dogs in Fig. 1 received a sodium adsorbing resin (SKF-648), 25 gm. per day, in their diet. Each rat also received as part of his low salt diet an average 0.33 gm. of this resin per day.

Hydration studies were made on the dogs before and after sodium depletion, the animals being hydrated through a Levine tube with 25 cc. of water per kg. of body weight per hour for 7 to 10 hours[4]. The urine output was measured hourly, and in the tabular data urine excretion is reported as the per cent output of the total hydrating dose at the end of the 7th hour. Hydrations were often continued beyond this time in attempts to produce the symptoms and signs of water intoxication. The rats received a dose of water equivalent to 6% of the total body weight[4]. Four such doses were given at hourly intervals and urine output was measured for a total of 7 hours. The urine outputs are reported in per cent of total hydration.

Blood samples were taken on the dog at the beginning and end of each hydration study. Samples of blood were taken from the heart of the rat at the end of the 7th hour. The serum sodium concentrations were determined with the Perkin-Elmer Flame Photometer. In determining the serum chlorides the Eisenman modification of the Volhard-Sendray[8] technique was used.

With this technique of paracentesis the serum sodium may be lowered a number of times and during each period of equilibration the hydration tests performed, thus allowing a comparison of urine output to various levels of serum sodium concentration.

Results. A. *Rate of excretion of water vs. serum sodium concentration in the dog.* Five dogs were studied and a definite correlation was obtained between the serum sodium concentration and the ability of the kidneys to excrete forced water (Fig. 1). For example, the 3rd dog with a normal serum sodium of 145 mEq. per liter excreted 68% of the administered water, but excreted only 22% when the serum sodium was decreased to 132 mEq. There are successive increases in urinary output in this dog as the serum sodium was allowed to increase. Every dog in this series responded in a similar manner.

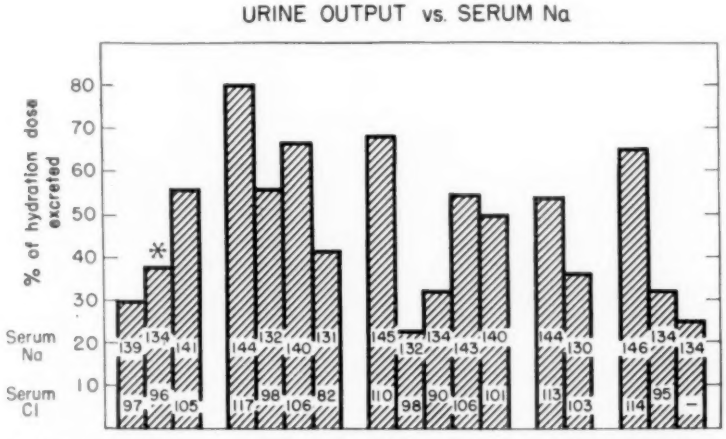

FIG. 1.—Relation of urine output to serum sodium in 5 dogs hydrated with water. Each group of consecutive bars represents the results obtained in a single dog. Serum sodium and chloride, in mEq. per liter, were determined just before the first hydration.

B. *Relationship of symptoms and signs to serum sodium level in the dog.* During the maintenance period after the sodium depletion, all dogs developed anorexia. The severity of the anorexia seemed to be related to the decrease in serum sodium. When the dogs were hydrated certain symptoms

* In this test the output represents a combination of vomitus and urine and is inaccurate regarding urine excretion alone.

and signs developed which were more severe in dogs with the lower serum sodium levels. The dogs developed nausea and vomiting, apathy, coarse fibrillary twitchings, generalized muscular irritability which in certain cases progressed to disorientation, convulsions, and finally, if salt was not administered, death. The greater the sodium depletion the more rapid the progression of the symptoms. In one dog at a serum sodium level of 139 mEq. signs of water intoxication did not develop until after the 10th hydration. The same dog with an initial sodium of 134 mEq. developed convulsions after the 8th hydration. In another dog with 124 mEq. of sodium only 6 hydrations were required to produce convulsions. These symptoms were not observed in normal animals even after 12 doses of water.

One of the dogs progressed spontaneously to the stage of coarse fibrillary twitchings and disorientation 48 hours after the second paracentesis. Its serum sodium concentration at that point was 118 mEq. These symptoms were relieved by administering hypertonic saline, intravenously.

C. *Urine output vs. serum sodium concentration in the rat.* A typical study of the effect of serum sodium on urine excretion in the rat is illustrated in Fig. 2. It can be seen that the urinary output decreased as the serum sodium was lowered. These studies differ from the dog in the fact that the rat serum sodiums were determined at the end of the 7th hour so that they are the result of salt depletion plus hemodilution. Nevertheless the serum sodium at this time always correlated with the urine excretion. The data obtained with 56 rats are summarized in Table 3. For comparison with the rat data serum sodiums were also determined in 22 instances in the dogs at the end of the 7th hour. These are compared in Fig. 3 and show a close correlation between the 2 species. As the serum sodium decreased in either the rat or the dog the urine output fell from normal control

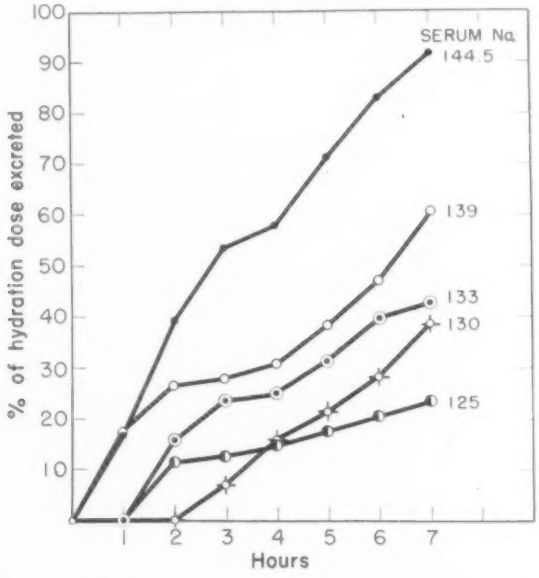

FIG. 2.—Relation of serum sodium to urine excretion in a typical test on hydrated rats. Serum sodium in mEq. per liter was determined at end of 7th hour.

values of 70% to values averaging 30%.

Discussion. In pre-renal failure, such as exists in cardiac failure, there is a retention of sodium which holds water and produces an increase in extracellular volume. Little has been said about the reverse of this situation, that is, just what might happen to renal excretion if the serum sodium concentration should be below normal. The value of sodium chloride restriction in patients with cardiac failure and in some with hypertension is well known. However, serum sodium may fall in such patients to levels that interfere with the excretion of urine, thus causing a retention of body water. A few such cases have recently been reported wherein patients being treated for cardiac failure eventually show an increased retention of fluids even though the serum sodium concentrations are quite low[1,2,6,10]. In the present study with the lower levels of serum sodium concentration in both the rat and dog, one can produce a marked delay in the excretion of administered water. These findings in the dog and rat are similar to those reported in man[10,11] and indicate that although initial dietary restriction of sodium chloride may aid in relieving edema, the serum sodium may fall to levels that interfere with urine excretion causing, instead, a reaccumulation of body fluids.

It is difficult to produce any symptoms in animals with normal serum sodium concentrations during water tolerance tests. In the salt depleted animal, however, one can readily produce signs of water intoxication, namely, anorexia, vomiting, apathy, coarse fibrillary twitchings, weakness, convulsions, and even death. These are the same signs as have been noted in the low salt syndrome of Schroeder[10] in human beings, and by Swingle *et al.*[12] in the dog. It is reasonable to believe that in decreasing the serum concentration of sodium, the chief extracellular electrolyte, one disturbs the osmotic equilibrium between the intra-extracellular fluid compartments, the latter becoming hypertonic, relative to the former. This means that fluid will shift into the cell.

A correlation between serum sodium and renal excretion may be noted in

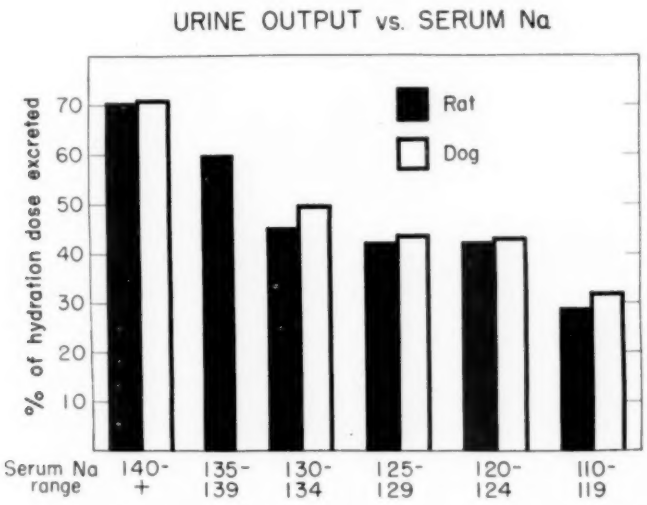

FIG. 3.—Summary of urine output obtained at various ranges of serum sodium, determined at end of 7th hour in the dog and rat.

adrenal insufficiency. In adrenal insufficiency with low serum sodium there is a marked decrease in ability to excrete forced water (Robinson-Power-Kepler Water Test)[9]. Signs of water intoxication may develop and can be relieved by the administration of sodium chloride. Dogs and rats in the present study, although having intact adrenal glands, show a similar correlation between serum sodium and urine excretion. The signs of water intoxication in such animals can also be relieved by the administration of sodium chloride, and this means of treatment should be used in patients on a low salt diet in whom the serum sodium concentration has fallen to low levels.

Summary. 1. Water tolerance tests were performed in animals with normal or low serum sodium values. In the dog and rat the reduction of serum sodium can markedly interfere with the excretion of the administered water. There is a definite correlation between the decrease in serum sodium and the amount of urine excreted.

2. There is a definite relationship between the serum sodium concentration and the rapidity of progression of signs and symptoms of water intoxication. As the serum concentration was lowered, fewer hydration doses of water were required to produce this intoxication.

3. The effect of low sodium on urine excretion in these animals is discussed in relation to the fluid retention and signs or symptoms that may occur in patients receiving a low salt diet.

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AN EVALUATION OF THE CUIRASS RESPIRATOR IN ACUTE POLIOMYELITIS WITH RESPIRATORY INSUFFICIENCY*

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Artificial respiration is the most vital therapeutic measure in preventing death from acute anterior poliomyelitis.

Standard tank, "iron-lung", respirators have usually been depended upon for effective artificial respiration in acute poliomyelitis but have the disadvantage of encasing the patient from the neck down, making him relatively inaccessible for nursing care, physical examinations and parenteral medication and feeding. They have an adverse psychological effect on the patient. A recently developed cuirass type respirator avoids many of these difficulties. It is applied only to the patient's anterior chest and upper abdomen. This type of respirator, accepted for limited emergency use by the Council on Physical Medicine of the American Medical Association[20], was given a clinical trial by the Poliomyelitis Service of the New York Hospital in 1949 after preliminary observations had indicated that it apparently produced adequate ventilation[8,17]. Further studies were made on this Service in 1950, comparing the effects of this respirator with tank respirators on patients convalescing from acute poliomyelitis with respiratory insufficiency.

Observations on these patients indicate that this type of cuirass respirator is not the mechanism of choice in administering artificial respiration to patients with acute poliomyelitis.

Methods. Clinical observations supplemented by blood and alveolar air analyses were made on 2 acutely ill poliomyelitis patients on whom the cuirass was used. Ventilation studies were performed on 5 convalescent poliomyelitis patients. Autopsies were performed on 3 patients who died following periods of 4 to 24 hours in the cuirass respirator.

Two identical cuirass respirators were used† (Fig. 1) consisting of a plastic shell which fitted snugly to the patient's anterior chest and upper abdomen. The plastic shell was enclosed within a rubber ring which could be inflated to prevent leaks between the patient's torso and the shell. Controlled positive and negative pressures up to 20 mm. Hg were supplied to the interior of the shell by an electrically driven pump which could have its rate controlled from 15 to 24 complete respiratory cycles per minute. Although the apparatus was designed to provide greater pressures, levels consistently higher than 20 mm. Hg were difficult to maintain without applying the shell so tightly that it caused excessive discomfort to the patient. The respirators used produced a Sine-wave type pressure curve.

Tank type respirators were standard Drinker and Emerson models. Arterial blood

* Aided in part by a grant from the New York Heart Association.

† Manufactured by The J. J. Monaghan Co., Denver, Colorado.

oxygen and carbon dioxide contents and oxygen capacity were determined with the Van Slyke-Neill manometric apparatus[16]. Venous plasma carbon dioxide combining powers were determined by the method of Peters and Van Slyke[15]. Additional oxyhemoglobin saturations were determined with the Millikan Oximeter[13]. Arterial blood pH's were determined in duplicate by the photometric method[23], or with a Beckman pH meter and glass electrode. Urine pH's were determined by sodium dinitrophenylazo-naphtholdisulfonate (nitrazine) paper.

Alveolar air samples were obtained through a tracheal catheter by repeated small collections at the peak of the positive pressure phase of several respirator cycles. Samples were analyzed in duplicate with a 0.5 cc. Scholander micro-gas analyzer[22] and alveolar p O_2 (partial pressure of oxygen) and p CO_2 (partial pressure of carbon dioxide) were calculated from the percentage composition of the gases in the samples. Serum sodium and potassium were analyzed with a flame photometer. Ventilation was measured with a Tissot gasometer using 3-minute expired air collections. Vital capacity was measured with a Sanborn closed circuit BMR spirometer calibrated by a Tissot gasometer. Maximum breathing capacity and residual air were determined by methods described by Baldwin *et al*[1].

Autopsies were done by members of the Department of Pathology, Cornell University Medical College.

Observations. Figure 2 demonstrates the clinical course of a 34-year old male who had spinal and bulbar paralytic poliomyelitis. His ventilation became insufficient shortly after admission to the hospital. He was nearly comatose at this time but not cyanotic. A cuirass respirator was applied, tracheotomy performed and a No. 5 tracheotomy tube with the inner cannula removed was inserted. Humidified oxygen was delivered directly to the tracheotomy tube by a No. 10 catheter with a multiple perforation tip at a rate of 6 liters per minute. Under this regimen the patient's color was good, and his lungs appeared to be well aerated on external chest examination. He remained in stupor for the next 5 days, and was only semilucid for the ensuing 4 days. He was febrile throughout this period.

Twelve hours after being placed in the cuirass respirator the patient's

FIG. 1.—The Cuirass Respirator.

venous plasma carbon dioxide combining power was greater than 85 vols./100 cc. and 24 hours later a similar elevation was noted. His urine pH at this time was highly acid. An arterial blood pH was 7.35, on the acid side of the normal range of 7.38 to 7.46[1].

Arterial oxygen saturations determined by blood gas and oximetric analysis were 95% or greater throughout the patient's course while he was receiving oxygen.

elevated. Following a period of increased shortness of breath during unassisted breathing, and with the realization that he suffered respiratory acidosis, he was transferred to a tank type respirator, run at a pressure of 15 cm. water and a rate of 16 per minute. This apparently increased his ventilation, for over the next 36 hours his carbon dioxide combining power fell from 73 to 56 vols./100 cc. Associated with this fall, there was a clearing in

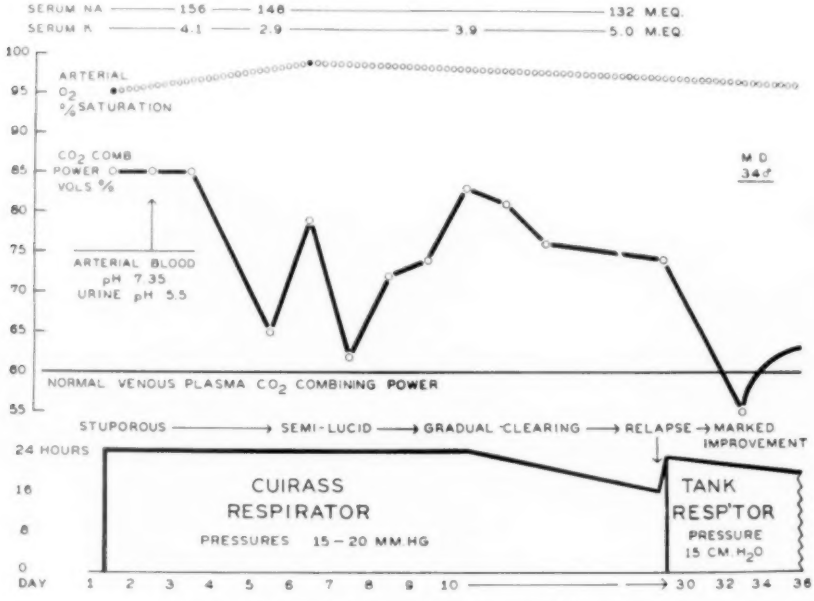
SERUM NA 156 148 132 M.EQ.
SERUM K 4.1 2.9 3.9 5.0 M.EQ.
ARTERIAL O2 % SATURATION
CO2 COMB POWER VOLS %
M.D. 34♂
ARTERIAL BLOOD pH 7.35
URINE pH 5.5
NORMAL VENOUS PLASMA CO2 COMBINING POWER
STUPOROUS → SEMI-LUCID → GRADUAL CLEARING → RELAPSE → MARKED IMPROVEMENT
24 HOURS
CUIRASS RESPIRATOR
PRESSURES 15–20 MM HG
TANK RESP'TOR
PRESSURE 15 CM. H2O
DAY 1 2 3 4 5 6 7 8 9 10 30 32 34 36

FIG. 2.—Hospital Course of a 34 year old male.

Because of his excellent oxygenation, it was not immediately realized that the high carbon dioxide combining power and blood acidosis in this patient were the result of insufficient pulmonary ventilation with inadequate carbon dioxide elimination. As a result he remained in the cuirass respirator until his 30th hospital day. Throughout this time, although he was gradually able to be without artificial respiration for as long as 8 hours a day, his carbon dioxide combining power remained

sensorium and improvement in sense of well being. Seven months after the onset of acute poliomyelitis this patient no longer needed artificial respiration and had a maximum breathing capacity of 49% of normal. His residual air was 194% of the expected normal volume. The residual air/total capacity ratio was 53% (normal 20%) indicating that he had developed pulmonary emphysema.

Figure 3 presents data obtained during the period of artificial respiration

on a 19-year old male with acute poliomyelitis who during the preceding 4 days in the hospital had demonstrated progressive spinal paralysis with decreasing ventilatory excursions. On his 5th hospital day he developed severe ventilatory insufficiency. The cuirass respirator was applied and oxygen administered by nasal catheter at 5 liters per minute. The following morning he was partially disoriented. He then lapsed gradually into coma. These

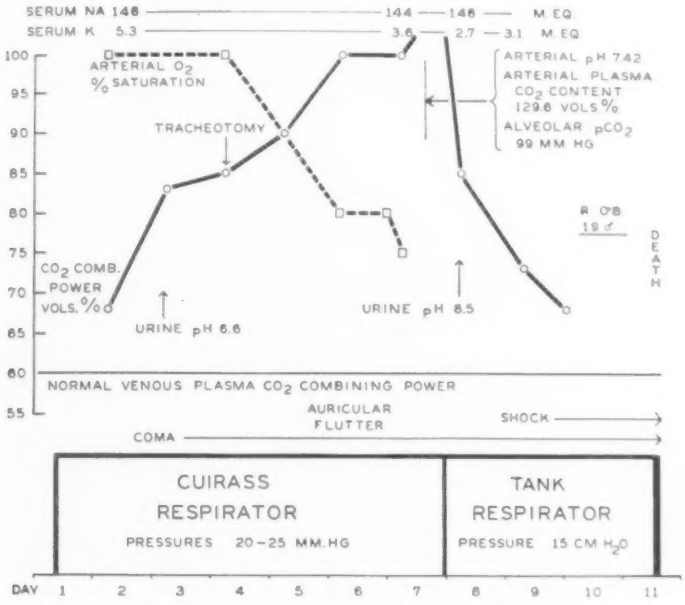

FIG. 3.—Hospital Course of a 19 year old male.

phenomena at the time were attributed to progression of his acute poliomyelitis.

The day after he was placed in the respirator his venous plasma carbon dioxide combining power was 68 vols. /100 cc. Arterial oxygen saturation on this and the next 2 days was 100%. During the ensuing 4 days in the cuirass respirator the venous plasma carbon dioxide combining power gradually climbed to 100 vols./100 cc. On the third respirator day a tracheotomy was performed because of progressive difficulty in keeping the airway free of obstructing secretions, and a No. 5 tracheotomy tube with the inner cannula removed was inserted. Humidified oxygen was delivered directly to the tracheotomy tube by a No. 10 catheter. On the 6th respirator day arterial pH was 7.42. At the same time the arterial plasma carbon dioxide content was found to be 129.6 vols./100 cc. over twice its normal level of 60 vols./100 cc. The alveolar air contained carbon dioxide at a partial pressure of 99 mm. Hg (normal 40 mm. Hg). The arterial oxygen had fallen to 80% saturation despite the continued administration of oxygen. Deep tracheobronchial suctioning failed to demonstrate any obstructing tracheobronchial secretions. It was evident that this patient's ventilation was insufficient either to oxygenate him or to eliminate adequate amounts of carbon dioxide from his alveoli. He was transferred to a tank respirator in an effort to increase his ventilation. This maneuver

was associated with a rapid fall in the venous plasma carbon dioxide combining power. At the same time urine pH increased to 8.5 as base was excreted by the kidneys and a diuresis of 3500 cc. occurred. This alkaline diuresis and fall in carbon dioxide combining power indicated that the patient was now eliminating carbon dioxide. However, he had been in coma for 4 days before this maneuver, had developed auricular flutter and hyperpyrexia, and had suffered irreversible damage. Three days after being transferred to the tank-type respirator, in spite of the improvement in ventilation, he developed vascular collapse and died.

COMMENT. Partially or wholly compensated respiratory acidosis due to failure of carbon dioxide elimination was not prevented in these 2 acutely ill patients when artificial respiration was attempted with the cuirass respirator. Both patients apparently increased their elimination of carbon dioxide when placed in tank respirators, indicating that their effective ventilation had been increased.

Measurements comparing the effects of the cuirass respirator and the tank respirator on convalescent patients with respiratory insufficiency are listed in Table 1. These 5 patients were able to breathe without artificial respiration for periods of from ½ to 16 hours. Each was well into convalescence when these studies were performed, and relatively out of danger from the standpoint of acute respiratory insufficiency. Each had a low resting tidal volume compared to the normal male adult tidal volume of 500 to 600 cc. and breathed with a marked increase in respiratory rate. Each had been in a tank respirator for at least 2 weeks and had, in addition, received artificial respiration on a fast rocking bed[18] for various periods of time. Each coordinated effectively with these different types of respirators. Observations were recorded only after several trials in the cuirass respirator when the patient had become accustomed to its action.

COMMENT. The data of Table 1 demonstrate that these patients achieved from 34 to 100% greater ventilation per respirator cycle in tank respirators than they did in the cuirass type at equivalent pressures. In fact, tank respirators produced from 15 to 41% greater ventilation per respirator cycle at −15 cm. H_2O pressure than did the cuirass respirator at the greater negative pressure of −20 cm. H_2O.

Moderate to severe anterior pulmonary emphysema was found at autopsy on 3 patients for whom the cuirass respirator was used before the above data on ventilation were available. These patients had cuirass respirator periods of from 4 to 24 hours preceding death and were in no other type of respirator. Since emphysema has been demonstrated in patients treated with tank respirators[10,12], these findings are not unique to treatment with the cuirass model. One of the 3, however, suffered severe abrasions from the rubber at the site of application of the chest piece and the prevention of such rubber burns in each acutely ill patient on whom the cuirass was used presented a significant nursing problem.

Discussion. Blood acidosis, with a high CO_2 content and low pH resulting from respiratory insufficiency, has received increasing attention in recent clinical literature[2,3,5,7,11,14,19]. When tidal volumes fall as the result of paralysis of the respiratory musculature, alveolar ventilation diminishes sharply. Near-normal minute volumes may be maintained by increasing the respiratory rate, but effective alveolar ventilation will not be maintained since with diminished tidal volumes a proportionately greater amount of each breath is required to fill the respiratory dead space. Thus, less inspired air flushes the alveoli, alveolar oxygen tension

falls and alveolar carbon dioxide tension rises. Because of the shape of the oxyhemoglobin dissociation curve, a relatively large reduction in alveolar oxygen tension must occur before a significant fall in arterial oxyhemoglobin saturation results. If a gas mixture rich in oxygen content is inspired, as when oxygen therapy is given, further protection against anoxemia is afforded.

In contrast to these factors which tend to prevent anoxemia when alveolar ventilation is reduced, an accumulation of carbon dioxide in the alveoli and blood can be prevented only by maintaining alveolar ventilation. Arterial blood pH is normally confined within the relatively narrow limits of 7.38 to 7.46 by the buffer system established between free carbonic acid (H_2CO_3) and bicarbonate ($BHCO_3$). According to the Henderson-Hasselbach equation, the normal arterial ratio of H_2CO_3/$BHCO_3$ $\frac{\text{carbonic acid}}{\text{bicarbonate}}$ equals 1/20. Since the tensions of carbon dioxide in the pulmonary alveoli and arterial blood are in close equilibrium[6,21], when alveolar carbon dioxide tension increases due to insufficient alveolar ventilation, arterial blood carbon dioxide (carbonic acid) concentration increases and the blood pH shifts to a more acid level. This may occur within a few minutes after a sustained fall in tidal volume.

Homeostatic compensation for this acidosis, and readjustment of blood pH to normal, is achieved by the kidneys excreting acid salts and conserving approximately 20 vols./100 cc. of bicarbonate for each vol./100 cc. of carbonic acid which accumulates. This compensatory mechanism is reflected by a rising carbon dioxide combining power, and is a relatively slow process involving wide changes in the extracellular fluid electrolyte pattern which may take days to complete. Even after readjustment of the blood pH, the elevated alveolar and arterial blood carbon dioxide tensions persist.

High concentrations of carbon dioxide in the blood result in hypertension[9], stupor, delirium, coma[7,23], and vascular collapse[3,4,23], phenomena frequently encountered in patients with respiratory paralysis associated with acute poliomyelitis. Therefore, artificial respiration

TABLE 1.—THE EFFECT OF THE CUIRASS AND TANK RESPIRATORS ON THE VENTILATION OF PATIENTS RECOVERING FROM ACUTE POLIOMYELITIS WITH RESPIRATORY INSUFFICIENCY

	Resting ventilation				*Cuirass*		*Tank*		*Increase in tidal volume*	
Pt.	*Rate per min.*	*c.c. Tidal volume*	*c.c. Vital capacity*	*Respirator pressure (cm. H_2O)*	*Rate per min.*	*c.c. Tidal volume*	*Rate per min.*	*c.c. Tidal volume*	*With tank over cuirass at equivalent pressures (−15+2 cm.)*	*With tank at −15+2 cm. over cuirass at −20+2cm. pressure*
				From To						
M. D.	44	183	370	−15 +2	15	260	15	488	88%	41%
34 M				−20 +2	15	345				
H. H.	32	274	915	−15 +2	16	625	15	945	51%	41%
28 M				−20 +2	16	670	15	1340	100%	
E. C.	32	283	460	−15 +2	16	365	15	490	34%	15%
16 M				−20 +2	16	427	15	610	43%	
O. H.	36	180	398	−15 +2	16	370	15	580	57%	20%
18 M				−20 +2	16	485	15	670	38%	
J. F.	30	280	490	−15 +2	16	411	15	612	49%	22%
21 M				−20 +2	16	503	15	720	43%	

to be effective must insure adequate elimination of carbon dioxide as well as physiological oxygenation.

Neither the absence of cyanosis nor the direct measurement of levels of arterial oxygenation within the normal range can be relied upon in completely evaluating the adequacy of respiration. This is demonstrated by the fact that both the acutely ill patients treated by the cuirass respirator had abnormally increased alveolar carbon dioxide tensions, calculated at greater than 71 mm. Hg in the the first and directly determined at 99 mm. Hg in the second. Arterial oxygen saturation remained high for at least part of the time that carbon dioxide was piling up in both. Both these patients suffered hypertension, delirium and coma during the period when their carbon dioxide tensions were elevated, and one died without ever recovering from coma.

The initial clinical impression that tank respirators achieve greater ventilation than the cuirass was confirmed in the studies on convalescents. In this group the tank respirator produced significantly larger tidal volumes than the cuirass in every patient.

Inadequate ventilation and respiratory acidosis can occur in some patients even in tank respirators[5,14] during the acute stage of poliomyelitis when muscle tightness and cryptic secretions reduce tidal volume, and fever and infection add to metabolic demands. Any device which achieves less ventilation than the tank, therefore, cannot be considered the agent of choice in managing patients in this stage of the disease. In this study, contrary to expectations, the cuirass respirator was found to achieve less ventilation than the tank respirators in every patient tested.

Complete analysis of the factors that reduce the efficiency of the cuirass in comparison to the tank respirator is beyond the engineering experience of the authors. Bedside observation, however, suggests that the shape of the cuirass itself is responsible. Thus during each inspiratory cycle the cuirass constricts the anterior chest at approximately the level of the 2nd to 4th rib and prevents full expansion of the postero-lateral thoracic wall from the level of approximately the 4th to 11th ribs. It seems to give mainly anterior pulmonary expansion in these areas which usually expand both anteriorly and laterally during inspiration in the tank respirator. In addition, during inspiration the cuirass compresses the lower abdomen and exerts negative pressure on the upper abdomen in order to lower the diaphragm. If gastric distention, which is frequently seen in patients acutely ill in respirators, is present, the inside of the shell at times actually compresses the upper abdomen, forcing the dilated stomach into the diaphragm and limiting inspiration in that way.

Therefore, only when the advantages offered by the cuirass are compelling, and when the amount of ventilation produced can be determined by spirometer to be sufficient, does it seem desirable to use this device in its present stage of development. Even when it produces adequate ventilation, the chest constriction which occurs would seem to limit the utility of the cuirass to short periods of time.

Summary. 1. The effects of a cuirass respirator have been evaluated on 10 patients with respiratory insufficiency due to acute poliomyelitis. Two patients were studied during their acute illness, 5 patients were studied during convalescence while they still needed artificial respiration, and 3 patients were examined at autopsy.

2. Blood acidosis, due to failure of carbon dioxide elimination from the lungs, was a manifestation of respiratory insufficiency in 2 acutely ill patients, and occurred in the absence of anoxemia.

3. Respiratory acidosis was not prevented or corrected in these 2 acutely ill patients by artificial respiration with a cuirass respirator, but was at least partially corrected by tank respirators.

4. Tank respirators produced from 34 to 100% greater tidal volumes at equivalent pressures than did a cuirass respirator on 5 convalescent patients with paralyzed respiratory musculatures.

5. Anterior pulmonary emphysema was seen at postmortem examination in the 3 patients who died following treatment in the cuirass respirator.

6. Only when the advantages offered by the cuirass respirator are compelling, and when the amount of ventilation produced can be determined to be physiologically sufficient, does it seem desirable to use this device in its present stage of development.

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CLINICAL IMPLICATIONS OF PRESSURES USED IN THE BODY RESPIRATOR*

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The body respirator, since its development for clinical use in 1929 by Drinker and Shaw[3], has been the most effective and widely used method for the prolonged treatment of respiratory paralysis. It has been referred to as an "ideal mechanical means of simulating normal costal respiration"[10], and "an imitation of the natural mechanism of respiration"[6]. The machine is generally believed to imitate normal breathing because the negative intratank pressure used is associated in the minds of most people with the normal negative pressure of the interpleural space.

In the published descriptions of the mechanical principle by which the respirator ventilates the lungs, the "vacuum" within the tank is spoken of as "expanding the thorax." It is a fundamental principle of physics that "vacuum" is a purely relative term and refers to the existence of a pressure lower than a reference pressure. When a "vacuum" appears to perform work, the work is in reality done by the reference (relatively positive) pressure. Recognition of this principle necessitates a re-statement of the manner in which the respirator produces respiration.

Fenn[5] and Henderson[8] have called attention to the fact that the negative pressure phase of the body respirator produces respiration in the same manner as positive pressure applied to the upper airway by the familiar devices for clinical application of pressure breathing. If this be so, then the deleterious effects of pressure breathing on the circulation[2] must be taken into consideration in the treatment of respiratory paralysis in the presence of circulatory instability. Moreover, if the types of respiration produced by a positive pressure apparatus and by the body respirator are equivalent, this fact would be of importance in considering the use of positive pressure appliances suggested for use simultaneously with the respirator[4,9].

The frequently observed failure of respirator users to recognize the comparability of the 2 methods led to a series of experiments which were designed to demonstrate graphically the effects on the circulation of pressure applied to the airway in the conventional manner and by means of decreasing the pressure around the patient's body.†

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† There is, of course, an air density difference between the 2 methods. Application of pressure to the upper airway will affect to a negligible degree the partial pressure of pulmonary gases and will cause a slight increase in tidal volume. In an adult with a functional residual volume of 3000 ml., the increase would be approximately 60 ml. per breath, if the added pressure went to 15 mm. Hg above the ambient pressure. Further, reduction of pressure around the body creates, in theory, a ventilating gradient somewhat sooner (by a few thousandths of a second) than positive airway pressure because of the greater speed of solid body than gaseous transmission.

REFERENCE POINT FOR PRESSURE MEASUREMENTS. The crucial point in the demonstration of the comparability of respiration produced by the 2 methods of establishing a pressure gradient is the question of base line. It is conventional to measure vascular and other pressures in the body with ambient pressure as the base line. For example, a person at sea level with an arterial blood pressure of 110/60 mm. Hg has, in absolute terms, a blood pressure of $\frac{110 + 760}{60 + 760}$; in other words, 110/60 above a base line of 760. When the individual moves to an area of reduced barometric pressure of, for example, 740 mm. Hg, his body tissues virtually instantaneously assume the new ambient pressure, and his blood pressure would be $\frac{110 + 740}{60 + 740}$ (still 110/60). Failure to change the base line for pressure measurement from 760 to the new ambient pressure of 740 would give the individual an apparent, but erroneous, blood pressure of 90/40. If one agrees, then, that pressures should be measured relative to the ambient base line, it is apparent that pressures in the respirator patient should be measured relative to the pressure inside the tank, and not relative to the atmospheric pressure. Fig. 1† demonstrates that the intratracheal pressure of a respirator subject is not a straight line, as it is usually visualized, but, when referred to the proper base line, is a positive pressure half sine wave which is the reverse of the negative intratank pressure curve. Fig. 2 represents intratracheal pressure when the method of artificial respiration is alternated between rubber bag compression with a standard anesthesia machine and the body respirator employing negative pressure. Only close scrutiny reveals slight differences, which are attributable to the inability of the operator to produce a perfect half sine wave by manual compression of the anesthesia bag. In Fig. 3 is seen a comparison of pulmonary artery and left auricular pressures during res-

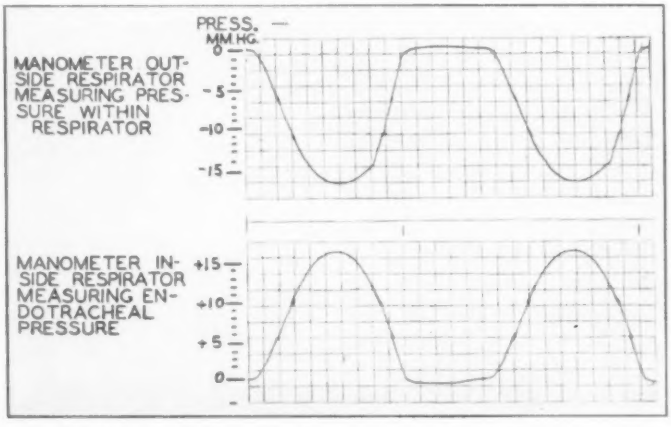

FIG. 1.—Lower tracing (dog) demonstrates that respirator patient is being subjected to positive endotracheal pressure.

† The pressures in all illustrations were measured with the Electromanometer, using a differential condenser microphone pressure pick-up, and recorded on a multi-channel direct-writing oscillograph, courtesy of the Sanborn Company, Cambridge, Mass.

piration by the 2 methods. The pressure changes in these portions of the vascular system are identical for the 2 methods when correct base lines are used.

THE BODY RESPIRATOR IN CIRCULATORY COLLAPSE. Barach, Fenn, Ferris and Schmidt[1] have summarized evidence for the existence of a number of compensatory mechanisms which combine to maintain adequate circulation in the presence of the increased intrathoracic pressure associated with pressure breathing in normal subjects. Chief among these mechanisms are an increase in peripheral venous pressure and peripheral vasoconstriction, both of which (in different manners) help to restore the normal pressure gradient from the peripheral veins to the right auricle.

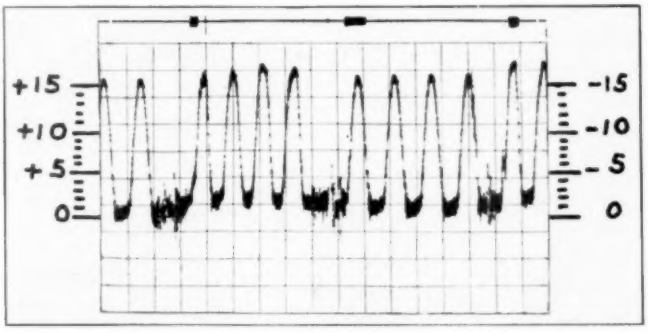

FIG. 2.—Endotracheal pressure (dog) in relation to subject's ambient pressure (manometer in respirator). Method of respiration alternated between negative respirator pressure and positive pressure with standard anesthesia machine. Change occurs at each signal marker. Scales: left, positive pressure by anesthesia machine; right, intratank pressure.

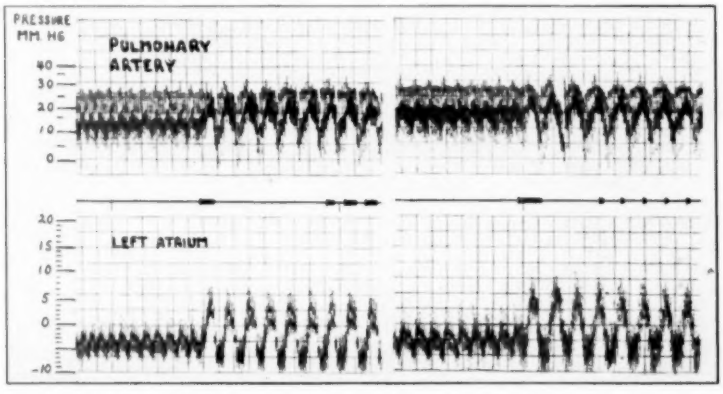

FIG. 3.—Anesthetized dog. At left: positive pressure breathing (+15 cm. H_2O by anesthesia bag compression) substituted for normal respiration at first signal marker. At right: body respirator (−15 cm. H_2O) begun at first signal marker. Manometer base lines at ambient pressure.

On the other hand, Carr and Essex[2] have shown that, in the presence of circulatory stress, positive intratracheal pressure is not well tolerated.

It was decided to investigate similarly the circulatory effects of the body respirator in dogs whose compensatory

circulatory mechanisms were compromised. The circulation was jeopardized by barbiturate poisoning, spinal anesthesia, or hemorrhage. In the first 2 methods, control of tone in the peripheral circulatory bed is largely lost; in the last method, the compensatory constrictor mechanisms of the peripheral vascular bed are employed in overcoming reduction in blood volume. Under each of these stress conditions, the additional burden of pressure breathing—whether applied in the usual manner or by use of the body respirator—produced a severe fall in systemic arterial blood pressure (Fig. 4). Clinical confirmation of these results has been obtained in a series of patients to be reported subsequently.

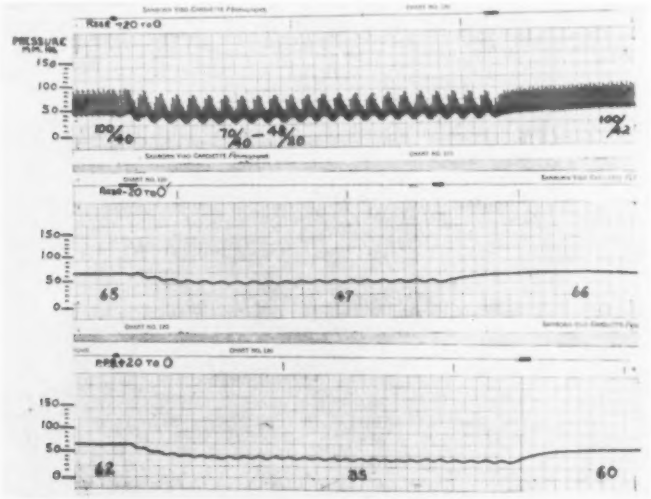

FIG. 4.—Femoral artery pressure in dog suffering from circulatory and respiratory depression due to barbiturate poisoning. Top: body respirator (−20 cm. H_2O to O) started at first signal, ended at second signal. Center: the same with electronically integrated mean pressure. Bottom: positive pressure breathing (+20 cm. H_2O to O) with anesthesia machine begun at signal mark.

USE OF POSITIVE INTRATANK PRESSURE. Negative intratank pressure causes the pressure in the thorax to be positive relative to the patient's body, and thus reduces venous return to the heart. A corollary postulate would be that positive intratank pressure causes the pressure in the thorax to be negative relative to the patient's body, and thus increases venous return and aids circulation. One might, therefore, expect that a respirator operated with a pressure range of −10 to +10 cm. H_2O would have a less deleterious effect on a failing circulation than a respirator operated with a pressure range of −20 to 0. Fig. 5 demonstrates that such is the case in an animal suffering from blood loss. When the combination of positive and negative intratank pressures is used on this animal, an even larger total ventilating gradient can be used without resulting in circulatory depression.

Seevers and Waters[10] have reported that the combination of positive and negative intratank pressures maintained the circulation of dogs under high spinal anesthesia much better than did either type of pressure alone. It is interesting to note that the use of combined positive and negative intratank pressures rather than the usual

negative pressure alone converts an intermittent positive pressure device to the physiologic equivalent of a "suck and blow" type of resuscitator.

Discussion. Appreciation of the mechanism of respiration in the body respirator allows one to apply the knowledge concerning positive pressure breathing to the patient who is being treated in the respirator. Circulatory changes that may occur are: *a*, impairment of the circulation (fall in blood pressure and decreased cardiac output); *b*, rise in venous pressure[1]; *c*, decrease in circulating blood volume (because of decreased capillary reabsorption of fluid due to higher pressure at the venous end of the capillary[1]; *d*, increased filling of the venous bed and arteriolar constriction[1]; *e*, increase in cerebral venous and cerebrospinal fluid pressures[7]. These effects become of considerable import when one considers the frequency with which circulatory collapse and cerebral edema occur in association with pathological conditions causing respiratory paralysis, *e.g.*, poliomyelitis and infectious polyneuritis.

Although enumeration of these circulatory changes may appear to constitute an indictment of the body respirator, it should be pointed out that the large majority of patients can be expected to tolerate 15 to 20 cm. of intermittent intratracheal positive pressure (that is, 15 to 20 cm. negative intratank pressure) without difficulty. Moreover, if circulatory depression occurs, the addition of positive intratank pressure (accomplished on most respirators by simple closure of a flap valve) should minimize the circulatory depression due to the respirator.

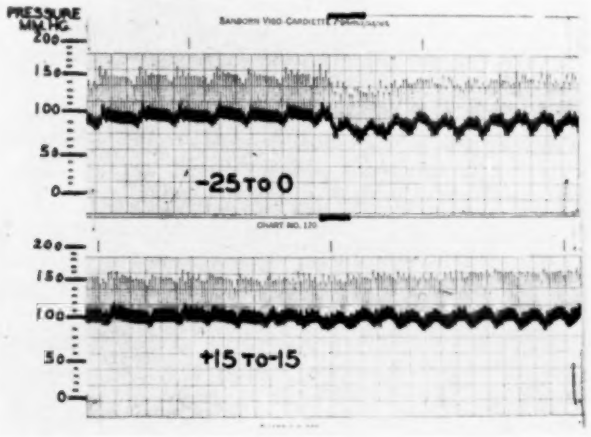

FIG. 5.—Dog with reduced blood volume due to hemorrhage. Respirator started at signal mark. Positive and negative intratank pressure prevents reduction of blood pressure.

The body respirator is an adequate method of giving intermittent positive pressure respiration without the use of a mask in, for example, the treatment of pulmonary edema. Wolfe and Murphy[12] were the first to report the use of the body respirator in the treatment of cardiac failure. Their patient, who had cardiac failure with orthopnea, dyspnea, and palpitation, was dramatically relieved by the respirator. As postulated by Werko[11], the reduced venous return and reduced output of

the right heart may be of value when the left ventricle working at maximum capacity is unable to maintain pulmonary venous pressure at a normal level.

Summary. Experimental evidence is presented to demonstrate that respiration produced by decreasing the pressure around the body (as in the body respirator), is physiologically and mechanically the same as respiration produced by increasing the pressure in the upper airway (as by a pressure dome over the head). The circulatory depression produced by the body respirator in the presence of a failing circulation may be profound; this effect can be minimized or averted by addition of a positive phase within the respirator. The use of negative intratank pressure is a method of giving positive pressure respiration without the use of a mask.

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MITRAL STENOSIS WITHOUT CLINICALLY DEMONSTRABLE LEFT AURICULAR ENLARGEMENT

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We have recently seen several patients presumably with mitral stenosis due to rheumatic heart disease in whom an enlarged left auricle could not be demonstrated by Roentgen-ray. We therefore undertook a clinical and pathological study to determine whether there are individuals in whom the classical lesions of mitral stenosis exist, but in whom roentgenological evidence of left auricular enlargement is absent. This hospital is well-suited for such a study since it is the recipient of large numbers of individuals with chronic heart disease.

Roentgen Manifestations of Left Auricular Enlargement. A brief review of the development of left auricular enlargement as noted on roentgenologic examination is given in order to call attention again to some of the variations in this process. In the order of appearance, enlargement of the left auricle occurs initially posteriorly, then to the right, superiorly, and to the left[9]. The earliest sign of left auricular enlargement is encroachment on the retrocardiac space, best seen in the right anterior oblique position, with compression or displacement of the barium-filled esophagus in its middle retrocardiac segment[4,7-9,11-13,15,17].

In the P-A view, the esophagus usually deviates to the right with left auricular enlargement. This occurs in part because the esophagus is eccentrically placed to the right of, as well as behind, the left auricle[2], and because of the concomitant right ventricular enlargement with resultant clockwise rotation of the heart (as seen from below)[9]. In the occasional instance where the esophagus is directly behind the summit of the left auricle, it will not be deviated in the P-A view[2], but may deviate to the left. Rarely, a normal left eccentric course of the esophagus is responsible for its deviation to the left, but more frequently it is the result of adhesions between the esophagus and an elongated transverse arch of the aorta. According to Schwedel[10], these adhesions are found in over 75% of adults at necropsy. When the aortic arch elongates due to disease processes, the esophagus may be deviated to the left in the P-A view, if these adhesions are present. Occasionally an enlarged right auricle is associated wth deviation of the esophagus to

the left, or there may be mediastinal adhesions pulling the esophagus to the left. When the esophagus deviates to the left, it will no longer be a border-forming structure with respect to the heart in the right anterior oblique position, and posterior displacement in the right anterior oblique position cannot be used as a criterion for left auricular enlargement[10]. When this occurs, other criteria for left auricular enlargement must then be relied upon, such as retrocardiac bulging in the right anterior oblique position, elevation or compression of the left main bronchus with widening of the tracheal angle[7,12,14], and double contour. With extreme left auricular enlargement, projection of the left auricle to the left beyond the pulmonary artery segment of the left mid-cardiac border may be seen. This is responsible for a double contour seen in the P-A view.

Postmortem Study. The records of all patients who at postmortem exhibited unequivocal mitral stenosis were reviewed. Thirty of these patients had satisfactory radiological studies during life. Of these, 24 were considered to have had an enlarged left auricle antemortem on the basis of roentgenologic findings. The 6 cases in which no left auricular enlargement could be demonstrated in life are briefly presented.

Case Reports. Case 1.—M. I., a 75-year-old white female, developed signs of cardiac failure at the age of 69 and was digitalized. There was no history of rheumatic fever. The blood pressure was 190/70. A systolic and a diastolic murmur were heard at the aortic area, as well as a systolic and occasional diastolic murmur at the mitral area. Regular sinus rhythm, later, auricular fibrillation, and terminally, nodal rhythm were noted on the electrocardiogram. Roentgenogram and fluoroscopy revealed no left auricular enlargement, despite an enlarged heart. The left mid-cardiac segment was concave. At postmortem, the heart weighed 380 gm. There was thickening of the left auricular wall, but the cavity was of normal capacity. The mitral and aortic valves were stenotic and insufficient.

Case 2.—W. E., a 58-year-old white female with no history of rheumatic fever, was admitted to this hospital in cardiac failure. Subsequently, several embolic episodes occurred. She later became febrile and subacute bacterial endocarditis was suspected, but repeated blood cultures were sterile. On physical examination, the blood pressure was 105/65 and a rumbling diastolic murmur was heard at the apex. The electrocardiographic findings included auricular fibrillation. No left auricular enlargement or displacement of the esophagus was visualized on fluoroscopy. The heart was enlarged with a convex left mid-cardiac segment on roentgenogram: Terminally, it was suspected that she had a ball-valve thrombus of the left auricle. At postmortem, the heart weighed 495 gm. The mitral valve was stenotic and the stigmata of subacute bacterial endocarditis were present. The left auricle was dilated, containing a large mural thrombus questionably ball-valve in type. The left auricular endocardium was thickened. Aortic valvulitis was also present.

Case 3. C. B., a 58-year-old white female, first experienced heart failure at the age of 52, at which time auricular fibrillation was discovered. There was a history of arthritis occurring at 30 years of age. Hypertension was present since the age of 47, and at the age of 57 she sustained a left hemiplegia. Pertinent physical findings included a blood pressure of 160/95 and systolic and rumbling diastolic murmurs at the apex. The electrocardiogram revealed auricular fibrillation. Roentgenograms disclosed a large heart with a convex left mid-cardiac segment. No enlargement of the left auricle was noted on fluoroscopy. At autopsy, the heart weighed 360 gm. The mitral valve was markedly stenotic. The left auricle was not specified as being large. In addition, there was tricuspid valvulitis.

Case 4. H. Z., a 68-year-old white male, had been in chronic congestive heart failure with auricular fibrillation for the previous 8 years. There was no history of rheumatic fever, although characteristic changes in the hands suggested rheumatoid arthritis. Examination never revealed a mitral diastolic murmur, but a harsh systolic murmur was heard at the apex. The blood pressure was 130/70 on admission, with subsequent fall in the diastolic pressure. The electrocardiogram confirmed the clinical impression of auricular fibrillation. No left auricular enlargement was noted on fluoroscopy but the heart was enlarged on roentgenogram with a straight left mid-cardiac segment. At postmortem the

heart weighed 760 gm. Both the mitral and aortic valves were stenotic and insufficient, and the left auricle was dilated.

CASE 5. F. B., a 51-year-old white male, with a record of 12 hospitalizations for congestive failure, had his first episode of failure and first knowledge of auricular fibrillation at the age of 37. There was no history of rheumatic fever. At the age of 50, several episodes of embolization occurred. The blood pressure was 140/70. Double murmurs were heard at the apex and the base. An enlarged pulsating liver was readily palpable. Auricular fibrillation was confirmed by the electrocardiogram. Roentgen studies revealed an enlarged heart with a straight left mid-cardiac segment but without enlargement of the left auricle. In the P-A esophagram, there was deviation to the left of the barium-filled esophagus just below the aortic indentation. At post-mortem, the heart weighed 640 gm. The pericardium was thickened and adherent. An adherent thrombus was attached to the thickened endocardium of the dilated left auricle. Stenosis and insufficiency of the mitral and aortic valves were marked. There was also tricuspid stenosis and insufficiency.

COMMENT. Of interest in this case was the fact that the esophagus deviated to the left in the P-A view, perhaps due to peri-aortic adhesions. For this reason, the right anterior oblique esophagram was of no value in judging left auricular enlargement. The absence of a double contour, of elevation of the left main bronchus, and of retrocardiac bulging were thought to rule out left auricular enlargement clinically.

CASE 6. L. B., a 39-year-old white female with a definite history of rheumatic polyarthritis, developed cardiac failure at the age of 24, and was digitalized. Auricular fibrillation was discovered at the age of 25. Numerous embolic phenomena occurred and there were several periods of hospitalization for recurrent failure. The blood pressure was 160/60. Systolic thrills and double murmurs were present at the apex and the base. Kyphoscoliosis of the thoracic spine was present. The electrocardiogram confirmed the clinical impression of auricular fibrillation. An enlarged heart with a convex left mid-cardiac segment was noted on roentgenogram. There was a large area of increased density at the upper and middle portion of the left cardiac silhouette in the P-A view which caused elevation of the left main bronchus in the P-A and left anterior oblique views. In the right anterior oblique position no left auricular enlargement was noted on fluoroscopy or on the esophagram. The course of the esophagus was straight in the P-A and left anterior oblique positions. At autopsy, the heart weighed 600 gm. The endocardium of the left auricle was thickened, and an adherent thrombus filled about one-fourth of a markedly dilated left auricular cavity. Marked stenosis and insufficiency of the mitral and aortic valves were present, as well as a tricuspid stenosis.

COMMENT. In retrospect, this case is an infrequent example of enlargement of the left auricle predominantly to the left with a double contour visible on the left cardiac border. Because of the straight esophageal course in the P-A view, it was felt that the esophagus was a border-forming structure in the right anterior oblique view. With the normal right anterior oblique esophagram, the left auricle was not considered enlarged antemortem according to the rigid radiological criteria described previously, but from the appearance of the roentgenograms the presence of a giant left auricle was correctly interpreted clinically (Figs. 1, 2, and 3).

At postmortem, co-existent mitral and aortic stenosis and insufficiency were present in 4 of the 6 cases, and 2 of the patients with aortic valvular disease also had tricuspid stenosis. In only 2 was mitral stenosis the only valvular lesion present. Of the 4 patients with aortic insufficiency, rumbling diastolic murmurs at the apex were heard in 3 during life. Consequently, with failure to demonstrate an enlarged left auricle radiologically, the impression of aortic insufficiency with an Austin-Flint murmur was justified ante-mortem in these patients.

CLINICAL STUDY. In the clinical phase of this problem, patients currently on our wards with mitral stenosis due to rheumatic heart disease were studied to determine how many failed to satisfy

FIG. 1.—(Case 11, Postmortem Series) P-A esophagram showing an enlarged heart with a circular area of increased density forming the left mid-cardiac segment. The left main bronchus is almost horizontal. Though not clearly visualized in this reproduction, the barium-filled esophagus is straight.

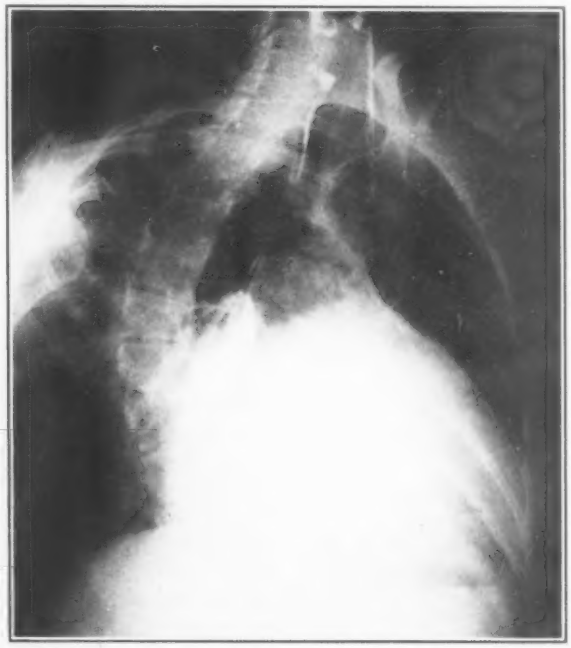

FIG. 2.—(Case 11, Postmortem Series) Right Anterior Oblique esophagram showing no posterior displacement of the barium-filled esophagus.

the Roentgen criteria for left auricular enlargement. Thirty patients were examined and no Roentgen evidence of left auricular enlargement was found in 7. A brief summary of the 7 cases follows:

CASE 6. J. N., a 49-year-old white male with a 4-year history of heart failure and no definite history of rheumatic fever, presented the following cardiac findings: a blood pressure of 140/80, a diastolic thrill at the apex, and systolic and rumbling diastolic apical murmurs. Auricular fibrillation was noted on the electrocardiogram. On roentgenogram, the heart was enlarged with a straight left mid-cardiac segment without deviation of the barium-filled esophagus in the P-A view. There was no evidence of left auricular enlargement on fluoroscopy or esophagram.

CASE 7. W. G., a 40-year-old colored male, noticed symptoms of cardiac failure at the age of 39. There was no history of rheumatic fever. On examination, the blood pressure was 130/80. Systolic and diastolic murmurs were heard over the mitral area and a systolic thrill was felt at the apex by some observers. On the electrocardiogram, in addition to regular sinus rhythm, the P wave in lead II was widened and the P-R interval prolonged. Teleoroentgenograms revealed an enlarged heart with a straight left mid-cardiac segment and no deviation of the barium-filled esophagus in the P-A or right oblique projection. No left auricular enlargement could be demonstrated on fluoroscopic examination.

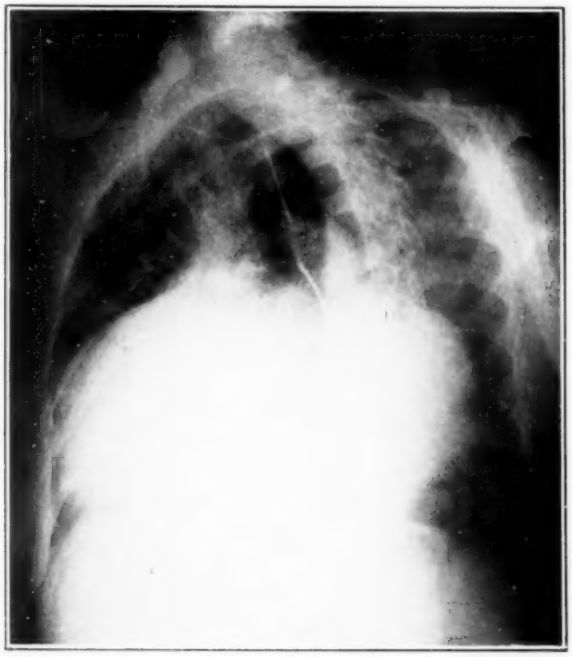

FIG. 3.—(Case 11, Postmortem Series) Left Anterior Oblique view showing the circular area of density to be the most posterior portion of the heart and to push the left main bronchus upward.

CASE 8. J. M., a 55-year-old white male, developed signs of cardiac failure at the age of 54 which responded to digitalis. There was no history of rheumatic fever. On physical examination, the blood pressure was 130/40. Systolic and diastolic thrills were palpable at the apex as well as a systolic thrill at the aortic area. At the apex, harsh systolic and rumbling diastolic murmurs were heard. A systolic murmur at the aortic area was transmitted to the neck and a soft early diastolic murmur was heard at Erb's point. The electrocardiogram revealed a regular sinus rhythm and a notched P wave in lead II. Roentgenograms and fluoroscopy in the P-A and oblique

positions disclosed an enlarged heart with a straight left mid-cardiac segment and no deviation of the barium-filled esophagus. There was no evidence of left auricular enlargement.

CASE 9. E. S., a 60-year-old white female with a definite history of rheumatic fever at the age of 20, sustained a left hemiparesis at the age of 54. Congestive failure ensued at the age of 57 and she was digitalized. Examination revealed a blood pressure of 170/80. A systolic thrill and double murmurs were present at the apex. The electrocardiogram confirmed the clinical impression of auricular fibrillation. Cardiac enlargement with a convex left mid-cardiac segment was noted on the teleoroentgenogram. Further Roentgen studies failed to demonstrate left auricular enlargement. Of interest was the fact that the barium-filled esophagus was deviated to the right as seen in the P-A view during the first examination, but on re-examination one month later deviation to the left in the P-A view was noted (Figs. 4, 5 and 6).

CASE 10. (J. C.) Hypertension and cardiac failure were first noted in this 62-year-old colored male at the age of 49, with many subsequent periods of hospitalization for cardiac failure. No history of rheumatic fever could be elicited. The blood pressure was 150/100. Systolic and rumbling diastolic murmurs were heard at the apex. A systolic thrill was palpable over the neck vessels and a rough systolic murmur maximal at the aortic area was transmitted to the neck. In addition an enlarged pulsating liver was palpable. The electrocardiogram revealed auricular fibrillation. On roentgenogram, the heart was tremendously enlarged with a concave left mid-cardiac segment. The barium-filled esophagus was straight in the P-A view. Left auricular enlargement was not demonstrated either by fluoroscopy or esophagram.

FIG. 4.—(Case 4, Clinical Series) P-A esophagram showing an enlarged heart with deviation of the barium-filled esophagus to the right.

CASE 11. J. H., a 59-year-old white male, has had several recurrences of congestive failure since the age of 56. Past history revealed polyarthralgia lasting 1 month at 49 years of age. The blood pressure was 120/70. Apical systolic and diastolic thrills, an apical systolic and a diastolic murmur, and a soft systolic murmur at the base were found on cardiac examination. Auricular fibrillation was present on the electrocardiogram. An en-

larged heart with a straight left mid-cardiac segment was found on a P-A teleoroentgenogram and there was no deviation of the barium-filled esophagus in this view. Fluoroscopy and esophagrams failed to demonstrate left auricular enlargement.

CASE 12. C. G., a 55-year-old white female with a definite history of rheumatic fever, was first digitalized at the age of 23. For the last 3 years continued heart failure necessi-

ogram disclosed an enlarged heart with a concave left mid-cardiac segment and deviation of the barium-filled esophagus to the left. No left auricular enlargement was noted on fluoroscopy or on the esophagrams. The left main bronchus was not elevated and there was no double contour.

The ages of these 7 patients ranged from 40 to 62 years, and a definite his-

FIG. 5.—(Case 4, Clinical Series) Right anterior oblique esophagram, showing no posterior displacement of the barium-filled esophagus. Both Figs. 4 and 5 were taken on the same date.

tated prolonged hospitalization. The blood pressure was 146/76. An apical systolic and a diastolic thrill were present, and a questionable systolic thrill was felt at the aortic area. A blowing systolic murmur and a rumbling mid-diastolic murmur were heard at the apex as well as a rough systolic aortic murmur and a blowing diastolic murmur at Erb's point. The electrocardiogram revealed auricular fibrillation. The P-A teleoroentgen-

tory of rheumatic fever was elicited in only 2. Three of the patients had coexistent aortic lesions and one of these also had involvement of the tricuspid valve. One had hypertension. Auricular fibrillation was present in 5 and regular sinus rhythm in 2. In the latter 2 cases the P waves were abnormal. All

patients had been in congestive heart failure one or more times and required digitalis. Each was considered a Class III cardiac patient.

Discussion. The demonstration of left auricular enlargement by radiological techniques is one of the necessary criteria for the diagnosis of mitral stenosis[5]. Parkinson has stated that in the diagnosis of mitral stenosis, enlargement of the left auricle is secondary in importance only to the characteristic diastolic murmur[6]. In a roentgenological (without the use of barium in the esophagus) and pathological study of 100 patients with mitral stenosis and insufficiency, Steel[13] reported enlargement of the left auricle as a constant finding. Nevertheless, some contrary reports have appeared in the literature[1,3,4].

It is conceded that mitral stenosis in its early stages may be present without left auricular enlargement. Nemet[4] emphasized the fact that occasional instances of mitral stenosis can occur in ambulatory children and in a smaller percentage of asymptomatic adults without demonstrable enlargement of the left auricle. Twenty-five cases of mitral valvular disease without cardiac enlargement were reported by Epstein[1]. Of these, 20 patients had no electrocardiographic changes and 24 had never been in failure. In a postmortem study of 61 hearts with mitral stenosis, Gouley[3] found 7 without left auricular enlargement.

FIG. 6.—(Case 4, Clinical Series) P-A esophagram taken 1 month later shows a slight leftward deviation of the barium-filled esophagus. Compare with Fig. 4.

Our study has been concerned with patients who had advanced rheumatic heart disease requiring prolonged hospitalization. The absence of Roentgen evidence of left auricular enlargement in this group with probably long established mitral stenosis would seem to have added significance. Failure to demonstrate left auricular enlargement radiologically during life occurred in 6 of the 30 patients in the necropsy

series, and in 7 of the 30 in the clinical series. Four of the 6 postmortem cases not exhibiting left auricular enlargement on antemortem examination did have an enlarged left auricle at autopsy. Therefore, unless terminal dilatation was the cause of the left auricular enlargement, no correlation existed between the size of the left auricle roentgenologically and anatomically in these 4 patients. Failure to demonstrate an enlarged left auricle despite the presence of auricular fibrillation in all 6 of the postmortem cases and in 5 of the 7 clinical cases is not in agreement with the findings of Sussman and Woodruff[16] who found marked enlargement of the left auricle radiologically in all of their 44 patients with auricular fibrillation due to rheumatic heart disease.

Of the patients described in our report, 3 of the 7 currently under treatment and 4 of the 6 in the necropsy group had co-existent rheumatic disease of valves other than the mitral. We are aware that there is difference of opinion concerning whether or not coexisting valvular lesions influence the development of the enlarged left auricle in patients with mitral stenosis. Perhaps in the future, data relating the effect of mixed valvular lesions upon left auricular enlargement as opposed to the effect of isolated mitral valve disease will be available.

Summary. 1. In a study of the case records of 30 patients with mitral stenosis due to rheumatic heart disease examined at necropsy, an enlarged left auricle could not be demonstrated in 6 by either fluoroscopy or esophagrams during life. In one instance, the presence of a giant left auricle was suspected from the appearance of the roentgenogram despite normal esophagrams.

2. In a comparable series of 30 patients thought to have mitral stenosis due to rheumatic heart disease currently under treatment at this hopsital, an enlarged left auricle could not be demonstrated in 7 either by fluoroscopy or esophagrams.

3. It is our opinion that failure to demonstrate enlargement of the left auricle roentgenologically should not deter one from strongly suspecting the presence of mitral stenosis if other clinical signs are present. The effect of mixed valvular lesions on left auricular enlargement has been briefly discussed.

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FEBRILE REACTIONS TO QUINIDINE

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The purpose of this paper is to report 2 cases of febrile reactions caused by the oral administration of quinidine sulfate.

Quinine was first used in the treatment of cardiac irregularities by Senac in 1749[8] and its use rediscovered by a patient of Wenckebach in 1914[11]. Frey[2] in 1918 found quinidine, the dextro-isomer of quinine, to be more effective in the treatment of cardiac irregularities and since then it has gained widespread use.

Untoward reactions to quinidine may be grouped into: 1) cinchonism, manifested principally by ringing in the ears, dizziness and gastrointestinal symptoms; 2) cardiac toxicity which may vary according to the underlying cardiac abnormality; 3) certain systemic reactions such as syncope, convulsions, collapse, and respiratory difficulty; and 4) acquired sensitivity manifested by rashes, thrombocytopenic purpura, and fever.

In 1942 Sturnick[10] reported a febrile reaction to quinidine which he believed to be the first reported case. However, Levy[5] in 1922 listed fever as an "unpleasant symptom" of quinidine administration. Siegal and Horn[9] recently reported 2 more cases.

Case Reports. Case 1. A. S., a 59-year old white male patient, entered the Baltimore Marine Hospital on October 11, 1949, for the 14th time in 2 years for conditions related to rheumatic heart disease. He did not recall any episode of acute rheumatic fever but in 1939 first noted dyspnea on exertion and was told he had heart disease. Dyspnea gradually increased so that in 1947 he became totally incapacitated. He was digitalized, placed on a low-salt diet and periodically given mercurial diuretics. The present admission was necessitated by attacks of palpitation and faintness. For a year he had been taking digitalis 0.1 gm. daily with an additional 0.1 gm. on alternate days, making a total of 0.3 gm. every 2 days. Examination revealed a poorly nourished man who was dyspneic at bedrest. The blood pressure was 108/84, the pulse 140 per minute and totally irregular, and respirations 24 per minute. Fundal veins showed pulsations synchronous with each heart beat. There were a few crepitant rales and some impaired resonance at the lung bases. The heart was grossly enlarged. Both systolic and diastolic murmurs were heard in the mitral and aortic areas and a systolic murmur in the tricuspid area. The veins of the neck were greatly distended. The liver was enlarged and tender, the margin being palpable just above the right iliac crest. There was a distinct swelling of the liver synchronous with each heart beat. There was slight pitting edema of the ankles. Laboratory studies revealed serologic tests for syphilis negative, white blood count 6250, hemoglobin 13.5 gm., platelet count 290,000, urinalysis negative, blood urea nitrogen 18 mg. per 100 cc. Electrocardiogram revealed auricular fibrillation, digitalis effect, frequent ventricular and nodal premature contractions and runs of tachycardia of undetermined origin. Roentgenogram of the chest revealed evidence of congestion ex-

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tending from the lung root regions and marked enlargement of the heart with a maximum transverse measurement of 19.8 cm. and an internal thoracic diameter of 29 cm.

The patient showed considerable improvement in his congestive failure on bedrest and continuation of his previous medications. It was thought possible that the paroxysms of tachycardia might be due to digitalis intoxication; therefore, digitalis was discontinued on October 15 and resumed at a rate of 0.1 gm. daily on October 27th. Paroxysms of tachycardia continued. These attacks, which lasted as long as 1 hour, were accompanied by faintness and on one occasion by unconsciousness resulting in a fall with laceration of the scalp. On October 28 quinidine 0.2 gm. 4 times daily was started. On November 5th his temperature rose, reaching a peak of 103.6° on November 9th. With the fever he developed nausea, vomiting and chills. The face became puffy and the skin hot and dry. The chest remained clear but the heart rate increased to 130 per minute. On November 10th numerous maculopapular erythematous areas about 3 mm. in diameter appeared on the lower chest, abdomen and flanks. Numerous petechial hemorrhages were noted about the ankles and feet. The liver was slightly smaller and less tender than on admission but the spleen had become definitely palpable and tender just below the rib margin. There was no lymphadenopathy. On November 9th and 11th the white blood count was 5000 with a normal differential count, the hemoglobin 13 gm. and the platelet count 228,000. All of 5 blood cultures were negative. On November 11th quinidine was stopped with prompt subsidence of all the significant symptoms enumerated above. On November 21st when 0.4 gm. of quinidine was given in a single dose there was an abrupt development of fever, the temperature rising to a peak of 103.8° in 8 hours and returning to normal after about 30 hours. There were no significant signs or symptoms accompanying this test dose (Fig. 1). The patient was later given a test dose of 0.6 gm. of quinine with no reaction. He gradually regained sufficient compensation to be discharged on December 20, 1949.

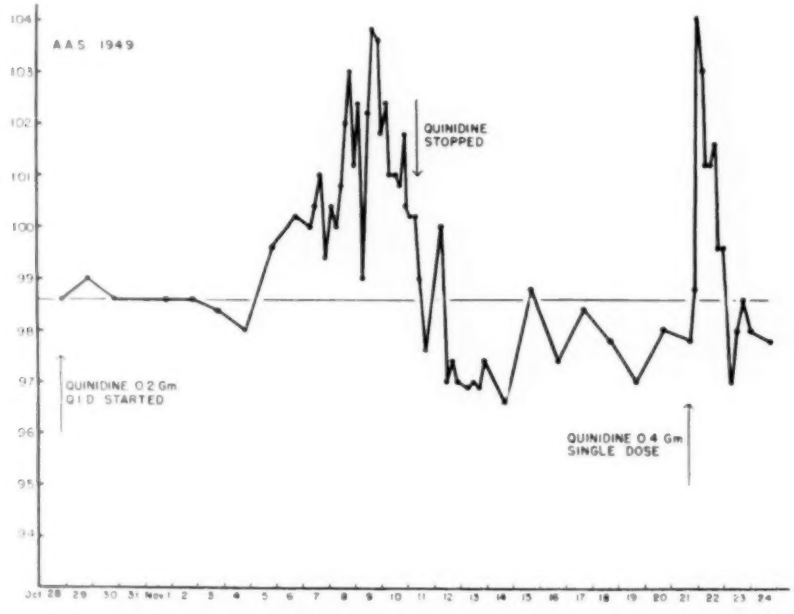

FIG. 1.—Temperature reaction in Case 1 to the therapeutic administration of quinidine and to a later test dose.

CASE 2. M. H. I., a 46-year old Coast Guard officer, first noted attacks of palpitation of 3 to 5 minutes' duration in 1930 following severe exercise and accompanied by a sensation of precordial tightness. Attacks

of this same description occurred approximately yearly until 1943 when they became more severe. In 1945 when hospitalized for renal colic an electrocardiogram showed Wolff-Parkinson-White syndrome which was confirmed on numerous subsequent tracings. In 1946 an attack of palpitation with pre-cordial pain radiating into the left arm lasted 30 minutes. Extensive examination revealed no evidence of myocardial infarction. In 1948 the attacks became more frequent and troublesome. On August 21, 1949, he was seen in the Out-patient Department of the Baltimore Marine Hospital, placed on fever, chills, profuse sweating and paroxysms of tachycardia, one of which was demonstrated electrocardiographically. On September 3rd quinidine was stopped. The temperature fell from 102.3° to 100.3° in 14 hours and reached normal in 24 hours. He was discharged on September 4th. For further evaluation he was admitted to the Baltimore Marine Hospital on September 15, 1949. History was as given and physical examination within normal limits. Laboratory studies were normal except for the electrocardiogram which again showed Wolff-Parkinson-White syndrome. On September 21st he

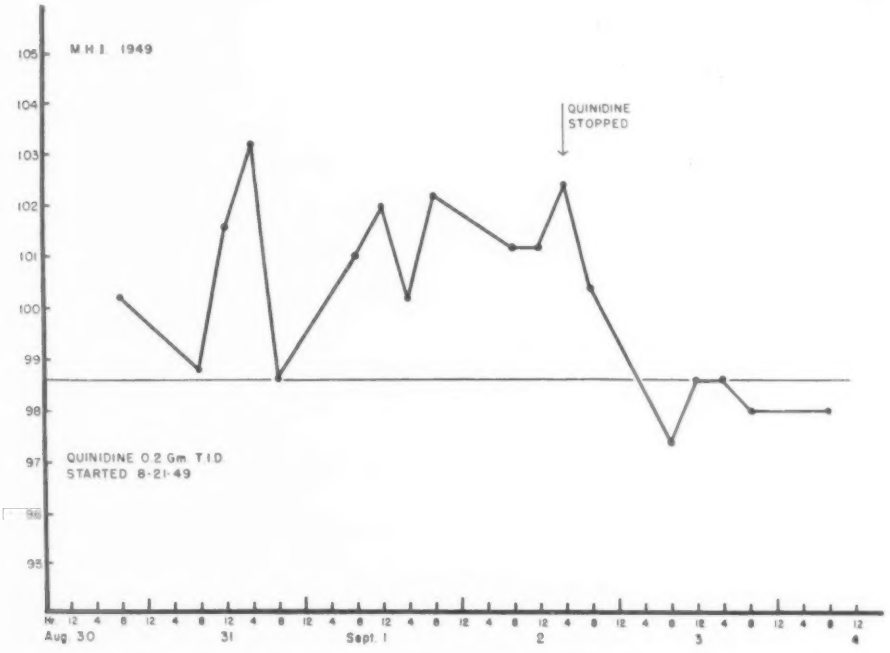

FIG. 2.—Temperature reaction in Case 2 to the therapeutic administration of quinidine.

quinidine 0.2 gm. 3 times daily. On August 29th he noted fleeting precordial pain followed shortly by chills and elevation of temperature to 103° (Fig. 2). He was given a sulfonamide and penicillin with no influence on the febrile course. On September 1st he was admitted to another hospital, at which time fever was the only abnormal physical finding. The white blood count was 8000 with 83% neutrophils, hemoglobin 14.5 gm. Blood culture, urinalysis and roentgenogram of the chest were all negative. While in that hospital he complained of pain about the mouth and teeth, buzzing in the ears, was given 0.8 gm. of quinidine between 8 a. m. and 6 p. m. At 2 p. m. the temperature was 98.6° and reached a peak of 99.8° at 9 p. m. after which it returned to normal, showing only a transient elevation the next evening. With the onset of the fever he noted "vibrations in the ears", headache and chilliness followed by a hot feeling. On September 24th he received 0.3 gm. of quinine every 4 hours for 4 doses. He did not develop fever but noted throbbing headache, ringing in the ears and nausea 5 hours after the last dose. He was discharged September 26, 1949, without medication.

Discussion. There are certain features which appear to be common to all the reported cases of fever due to quinidine. The onset of fever and accompanying symptoms appeared several days after the drug had been started, generally about a week. They subsided within several hours after withdrawal of the drug. Subsequent single doses caused a much more prompt rise in fever, usually within a few hours. This suggests that the individuals acquired an abnormal sensitivity.

It is not known whether Case 1 would have developed sensitivity to quinine on prolonged administration but it does seem reasonably obvious that he was not sensitized to quinine by the administration of quinidine. While it is not certain, it is suspected that Case 2 may have been sensitized to quinine by the administration of quinidine. Fever did not develop, though early symptoms of cinchonism did. Neither case is known to have taken quinine or quinidine prior to the described episodes.

Case 1 developed a maculopapular rash, petechial hemorrhages and splenomegaly without thrombocytopenia (anaphylactoid purpura). Cases of thrombocytopenic purpura due to quinidine[7] have been reported. Generalized eruptions as well as localized eczematous reactions have also been reported[3]. Breu and Zollner[1] described fatal anaphylactic shock from quinidine.

Needless to say, if one does not consider quinidine as an etiologic factor in these cases the diagnostic problem is extremely confusing. In patients who develop sensitivity to quinidine one must rely on quinine, digitalis, procaine amide[4,6] and other agents, depending upon the indications in the individual case.

Summary. Two cases of febrile reaction to quinidine sulfate administered orally are presented.

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THE ROLE OF THE LIVER IN THE DETOXIFICATION OF TETRAETHYLTHIURAM DISULPHIDE (ANTABUSE)

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Tetraethylthiuram disulphide (Antabuse) has been tried experimentally in the treatment of alcoholism in Denmark, Sweden, Great Britain, the United States and Canada since the discovery of its possible value for this addiction was made in 1948. The limited information available upon this drug has been reviewed and summarized, for example by Glud[6], and by Dale and Ebaugh[2]. Antabuse is not expected to be available for general sale in the United States until about the summer of 1951[3], and Canadian physicians have been cautioned that the drug is potentially dangerous[5]. Death following administration of Antabuse has been reported[9]. These facts emphasize the need for further investigation into the pharmacology and toxicology of Antabuse.

The work to be described in this report, was done with the view of obtaining information upon the role of the liver in the detoxification of Antabuse. In 1948, Hald *et al.*[7] reported that Antabuse was slowly eliminated from the body, did not appear in urine and was present in small amounts in the feces, evidence suggesting that the drug could possibly be broken down in the liver. Edwards[4] found that the oxygen consumption *in vitro* of rat liver homogenates was inhibited by Antabuse, and Nowinski *et al.*[10] noted that this inhibition could be nullified by addition of ascorbic acid, which suggested that Antabuse may act as a competitive hydrogen acceptor. Glud[6] stated categorically that Antabuse should not be given to a patient having less than 85% of normal function of the liver. In the work to be described below, it was found that partial hepatectomy lowered the resistance of albino rats to administration of toxic doses of Antabuse. This information indicates that Antabuse may be detoxified by the liver.

Method. Albino rats of 200 to 350 gm. body weight were anaesthetized with ether, laparotomized, approximately 75% of the liver removed, and the abdomen closed, the entire operation taking about 15 minutes. Most of the animals survived this operation, a few deaths occurring within the first 24 post-operative hours. Only animals alive and healthy 36 hours after operation were used for further study. At this time the required dose of Antabuse was suspended in Acacia Mucilage, U.S.P., and given by stomach tube. Food, which had been withheld since before operation, was then allowed and the animals observed daily for 3 weeks. Autopsies were performed upon all rats that died.

The Antabuse used was pure, crystalline tetraethylthiuram disulphide.* Preliminary experiments indicated that the LD50 of this material given by stomach tube to normal rats was approximately 4 gm. per kg. body weight, which is of the order of that found by Child[1].

*Provided by Ayerst, McKenna and Harrison Limited of Montreal through the courtesy of Dr. John B. Jewell.

After some initial trials with a wide range of doses of Antabuse, the doses finally selected for study were 4.0, 5.0 and 6.0 gm. per kg. of body weight.

In a parallel control series of experiments, the rats were laparotomized, the liver manipulated but not cut, the abdomen closed and Antabuse administered in the same doses as to the sub-totally hepatectomized rats. The results obtained in this control series will be described below. Two other control groups were used to check the mortality rate from the above 2 operative procedures alone. In one of these, 16 albino rats were sub-totally hepatectomized and given no Antabuse; there were no deaths in this group. In a 2nd group, 15 albino rats were laparotomized and given no Antabuse; there were likewise no deaths in this group. Hence any deaths in the Antabuse treated animals could be ascribed with reasonable certainty to the Antabuse alone.

Results. The signs and symptoms following administration of these toxic doses of Antabuse were qualitatively similar in the sub-totally hepatectomized rats and in the laparotomized controls. The usual sequence of reactions appeared a few hours to a day or two after giving antabuse. Frequency of urination, dacryorrhea and chromodacryorrhea usually appeared together and early, frequently followed by rhinorrhea and blood-tinged secretions. The animals became progressively more lethargic and slow in their movements. They rested and walked with the back humped and when they moved, they tended to hold their legs under their bodies. The eyelids were drooped. Many animals had diarrhea which was followed by constipation, while others were constipated throughout. Their cages had a fairly characteristic foul smelling odour. They lay quietly, apparently asleep, for long periods, even at night when rats are normally active. There was a progressive loss in weight, listlessness, a slowing of the cardiac and respiratory rates and a tendency toward paralysis of the hind limbs characterized by dragging of the hind limbs when attempting to walk.

The death rate and the interval before death varied in the 2 groups and will be described below. At autopsy the animals were noted to have lost weight. The stomach often contained some Antabuse crystals, the contents were occasionally blood-tinged, the mucosa was inflamed and covered with numerous small, brownish black ulcerated areas. The duodenum was also ulcerated. The liver had a pale colour and a cellular appearance. The lungs appeared to be congested and slightly hemorrhagic.

Data upon death rates in hepatectomized rats and laparotomized controls are summarized and presented in Table 1. The mortality rate was consistently higher in the hepatectomized rats. Thus, a dose of 4 gm. of Antabuse per kg. body weight killed 76% of hepatectomized rats and only 50% of the laparotomized controls. The difference of 26% was calculated after Hill[8] to have a standard error of 14, which indicates that the odds were approximately 1 in 20 that it could have occurred by chance. Following administration of the 5.0 and 6.0 gm. per kg. doses of Antabuse, death rates were also higher in the hepatectomized rats, and the statistical possibility that the difference could have been due to chance was less than with the 4.0 gm. dose.

The number of days between administration of Antabuse and death was consistently and significantly less in the hepatectomized rats than in the laparotomized controls, a further indication that the hepatectomized rats were more susceptible to the toxic and lethal effects of Antabuse. Data upon these survival times in rats which succumbed to Antabuse are summarized and presented in Table 2. The hepatectomized rats may be seen to have lived only one-quarter to one-half as many days as did the laparotomized controls. The standard error of the

mean difference in days of survival was calculated after Hill[8] and may be seen to be one-third or less of the mean difference in each dosage group. This indicates that the mathematical odds that the difference was due to chance were of the order of 1 in 400 or less.

Thus, it may be concluded that these experiments demonstrate within reasonable limits of surety that hepatectomy increases the susceptibility of albino rats to the toxic and lethal effects of Antabuse. Conversely, this evidence may be taken to indicate that Antabuse is, in part at least, destroyed with the aid of the liver, possibly in the liver, and that the liver plays a role in the detoxification of this drug.

TABLE 1.—THE EFFECT OF SUB-TOTAL HEPATECTOMY UPON THE MORTALITY RATE OF ALBINO RATS FOLLOWING ADMINISTRATION OF TETRAETHYLTHIURAM DISULPHIDE

	Death Rate					
	Sub-totally Hepatectomized Rats		*Laparotomized Controls*		*Mean Diff.*	*Standard Error of Mean Difference*
Dose of Drug gm./kg. Body Wt.	*No. of Animals*	*% Dead*	*No. of Animals*	*% Dead*	*%*	*%*
4.0	21	76	20	50	26	14
5.0	21	95	20	60	35	12
6.0	21	95	20	70	25	11

TABLE 2.—THE EFFECT OF SUB-TOTAL HEPATECTOMY UPON THE SURVIVAL TIME OF ALBINO RATS FOLLOWING ADMINISTRATION OF TETRAETHYLTHIURAM DISULPHIDE

	Survival Time					
	Sub-totally Hepatectomized Rats		*Laparotomized Controls*			*Standard Error of Mean Difference (Days)*
Dose of Drug gm./kg. Body Wt.	*No. of Animals*	*Days until Death (mean)*	*No. of Animals*	*Days until Death (mean)*	*Mean Diff. (Days)*	
4.0	16	4.4	10	8.1	3.7	1.2
5.0	20	2.4	12	6.6	4.2	0.87
6.0	20	2.0	14	9.3	7.3	1.2

Summary. Tetraethylthiuram disulphide (Antabuse) was administered by stomach tube, 36 hours after operation, in doses of 4.0, 5.0 and 6.0 gm. per kg. body weight to 63 sub-totally hepatectomized albino rats and to 60 suitably laparotomized but not hepatectomized controls. Thirty-one other control rats were similarly operated upon but not given Antabuse at 36 hours post-operatively; none of these died.

The mortality rates ranged from 76 to 95% in the sub-totally hepatectomized rats, and from 50 to 70% in the laparotomized controls receiving Antabuse, the P value of the differences being 0.05 or less.

The mean number of days' survival after Antabuse ranged from 2.0 to 4.4 in the sub-totally hepatectomized rats and 6.6 to 9.3 in the laparotomized controls, the P value of the mean differences being less than 0.01.

It was concluded that these results indicate that Antabuse was detoxified by the liver in these experiments.

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HEMOLYTIC ANEMIA ASSOCIATED WITH LIVER DISEASE

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Since the initial discussion of Eppinger[7], liver disease and especially cirrhosis has been repeatedly listed as an occasional cause of hemolytic anemia [3,22]. Yet it has never been clear whether severe disease of the liver predisposed a few patients to the development of an acquired hemolytic anemia of the "symptomatic type"[16] or whether certain types of hemolysis, by overburdening the liver, led to necrosis of hepatic cells and at times to cirrhosis.

It is well recognized that Laennec's cirrhosis may be accompanied by a macrocytic anemia, but Wintrobe[23,24] found the anemia generally to be mild or moderate. Fellinger and Klima[9] also found the anemia in cirrhosis to be usually mild, but described a reticulocytosis of 10% or more in half of their cases. The difficulty of excluding at least contributory effects of: 1) intermittent bleeding of esophageal varices, 2) hypersplenism associated with portal hypertension, and 3) malnutrition, in such cases, is apparent.

Reviews of acquired hemolytic anemia mention liver damage as a possible complication. Thus Dameshek and Schwartz[5], collecting cases of the acute type from the literature, mentioned the frequency of hepatic enlargement and hemosiderosis at autopsy. Mason[14] stated that some of the chronic cases "die of a combination of anemia and hepatic insufficiency with marked fibrosis of the liver". He suggested, however, that many of these had calculi and an obstructive jaundice. It is noteworthy, however, that chronic hemolytic processes alone do not seem to lead to significant liver damage. Thus, Meulengracht[6] mentions that there are "no significant pathologic-anatomical changes in the liver itself" in chronic hereditary hemolytic jaundice, and Sturgis[19] states that the liver is usually normal in sickle cell anemia and congenital hemolytic anemia. Liver disease with fatty degeneration of the cells may be seen in only one such condition, Cooley's anemia[1], which has not been included in this paper. In all hemolytic anemias, uncomplicated hemosiderosis may be found at autopsy to involve the liver, but it is usually difficult to differentiate the role of transfusion in its causation[15] from that of intrinsic red cell destruction.

Our attention has been called to the association of hemolytic anemia and severe hepatic disease by the occurrence within the past year of 3 cases in the Presbyterian Hospital. All of these showed alarming degrees of hemolytic anemia, with clinical liver disease substantiated by biopsy. It is the purpose of this report to present these cases in detail, as well as to summarize additional cases from the hospital records.

Case Reports. Case 1. J. G., a 31-year old nurse, was first admitted to Presbyterian Hospital in September, 1949, for icterus and

extreme pallor. There was a questionable story of recurring yellow sclerae in childhood but no history of familial icterus. In 1943 she was said to have been run down, underweight and anemic, but improved with rest, liver injections and oral iron. Her spleen was palpable. In 1945 marked pruritus was present from the 3rd to the 9th month of her only pregnancy. Three months postpartum, anorexia, associated with mild jaundice, appeared for 3 weeks, though she had not been transfused. Moderate hepatomegaly, an increased delayed serum bilirubin, and a low-grade anemia were first noted at this time and persisted thereafter.

In June, 1949, she was admitted to another hospital because of fatigue and dyspnea, and was found to have marked pallor and icterus, a few ecchymoses, a liver palpable 5 cm. below the costal margin, and a spleen extending to the umbilicus. Active hemolysis was indicated by a red blood cell count of 2,100,000, a hemoglobin of 8 gm., reticulocytosis of 24%, and increased fecal and urinary urobilinogen. There was no evidence of hemorrhage. After 6 whole blood transfusions, she was transferred to Presbyterian Hospital for splenectomy. Additional laboratory findings preoperatively included a spherocytosis of 10%, a definite increase in red cell fragility, increased normoblastic erythropoiesis of the bone marrow, and a negative Coombs test. The cephalin flocculation test was +++, thymol turbidity ++, bilirubin 9 mg. per 100 cc. direct, and alkaline phosphatase 16.4 Bodansky units.

A 2600 gm. spleen was removed, which revealed congestion and extramedullary hematopoiesis on section, consistent with the diagnosis of hemolytic jaundice. An enlarged, pebbly firm liver was described, in which, on biopsy, extensive cirrhosis was found. Twenty transfusions of 500 cc. each had been given and hemosiderosis was noted in both organs.

Clinical improvement was slow but gratifying, with decrease in the jaundice and stabilization of the hemoglobin at 10 gm. until the 12th postoperative day, when a severe hemolytic crisis supervened. Associated with a fall in hemoglobin to 5.5 gm. was a rise in reticulocytes to 31%, and nucleated red cells to 137 per 100 white cells. Two transfusions were given with partial stabilization of the patient's condition. The serum bilirubin reached a level of 30.7 mg. per 100 cc., and the alkaline phosphatase 34 Bodansky units. A positive Coombs test was found, which has persisted since then. A course of ACTH therapy was started with the hope of inhibiting the presumed antibody-antigen reaction and also the lymphocytic infiltration of the liver. Over a 6-day period, a total of 350 mg. was given, which was followed by continued clinical improvement with stabilization of the hemogram, fall of the bilirubin level to 12.5 mg. and cephalin flocculation to 1+, leading to her discharge.

After an interval of 8 weeks, progressive hemolysis recurred, climaxed after 7 weeks by extreme pallor, dyspnea and icterus unrelieved by transfusion, and necessitated her second Presbyterian Hospital admission on January 5, 1950. The hemoglobin had fallen to 4 gm. with 60% reticulocytes, 150 nucleated red cells per 100 white cells; the Coombs test was ++++, as was the cephalin flocculation. The serum bilirubin was 46 mg. direct, cholesterol 560 mg., and alkaline phosphatase 12 Bodansky units. Four transfusions were given without effect, and in view of the critical situation, cortisone therapy was started and continued for 4 weeks at 50 mg. intramuscularly every 12 hours. A detailed report of the results by Hanger and Collins[2] is now in press. Fever subsided promptly and clinical improvement was striking. There was improvement in the liver function tests, although hepatic biopsies before and after therapy were unchanged. The nucleated red cells disappeared from the peripheral blood, reticulocytes fell to 9%, hemoglobin rose to 11 gm. without further transfusion, and the Coombs test decreased to ++. She was discharged with the diagnosis of coarse nodular cirrhosis and acquired hemolytic anemia. She did moderately well at home with a persistent mild jaundice without fever. At the end of 5 months she had not required further transfusion, although her hemoglobin had slowly fallen to 6 gm. Shortly thereafter she was readmitted for another course of cortisone therapy, again with a very satisfactory response, without transfusion. On discharge her hemoglobin had risen to 12.3 gm. Since then for 6 months she has been on maintenance cortisone and continues in fair health with a normal hemoglobin. Her most recent serum bilirubin was 10 mg.

Case 2. C. W., a 54-year old housewife, was first admitted to Presbyterian Hospital in 1945 after therapy with liver extract, oral iron, and 5 whole blood transfusions had failed to relieve her complaints of progressive weakness, fatigue, weight loss and painless jaundice over a 2-year period. There was no family history of anemia or jaundice. She appeared chronically ill with jaundice, pallor and some skin pigmentation. Moderate cardiac enlargement was associated with a soft,

TABLE 1.—CASES OF HEMOLYTIC ANEMIA AND PROVEN LIVER DISEASE

	Name Sex	Age	Hgb. (gm.) / RBC × 10⁶ (lowest)	RBC fragil.	Coombs test	Nucl. RBC/100 WBC	Retics. % / Spherocytes	Liver enlargement*	Ceph. / Thymol.**	Bilirubin†	Prothromb. time (secs.)¶	Alk. phosphatase§	Alb. / Glob. (gm.)††	Splenectomy / response	Liver biopsy	Follow-up	Notes; No. of transfusions (Tr.)
1)	J. G F	30	4.0 / 1.18	incr.	++++	155	90 / yes	yes	++++ / +++	25D	—	29	4.2 / 2.7	yes / slight	extens. cirrhosis	impr. after cortisone 2×	26 Tr. in 6 months
2)	C. W. F	58	8.5 / 1.8	incr.	+++	3	19 / yes	yes	+++ / ++++	7D	22	22	3.1 / 3.7	yes / none	diff. swelling of cells	died 5 yrs. after splenect.; ascites, hematem., jaund.	at operation, liver grossly cirrhotic; BSP 35% after 30 min.; 3 Tr.
3)	W. R. F	18	9.5 / 2.8	norm.	0	200	19 / no	no	++++ / ++++	5I	26	3.9	3.0 / 2.9	yes	cirrhosis, periport. necrosis	spont. remission anemia; liver dis. persists	prior splenectomy for varices; 0 Tr.
4)	B. K. F	33	3.5 / 0.9	—	—	9	24 / no	yes	++++ / —	2.5I	—	—	3.8 / 1.5	yes / none	central congest., focal necrosis, hemosid.	died; anemia, cardiac fail.	20 Tr. in 2 mos.
5)	H. R. F	64	2.6 / 0.9	norm.	—	3	60 / no	yes	++++ / —	0	29	2.0	3.9 / 2.0	no	focal necrosis, hemosid.	died; anemia, card. fail.	2 Tr.
6)	J. B. M	1	4.5 / 1.6	incr.	++++	15	27 / yes	yes	a) — / b) +++ / ++++	a) 6.8I / b)24 D	a)17.7 / b)18.0	a)12 / b)12.2	a) — / b)2.8 / 1.5	yes / none	a) hemosid., necrosis / b) fibrosis also	probable serum hepatitis on 2nd adm.; died; anemia, rhobemia	a) & b) zinc and phenol turbid. 15 u. (elevated); 42 Tr. in 9 mos.
7)	P. C. F	36	1.4 / 0.6	incr.	—	90	51 / yes	yes	—	7.1I	—	—	4.4 / 1.7	yes / none	central congest., focal necrosis, hemosid.	died; anemia, card. fail.	11 Tr. in 10 wks.
8)	M. S. F	10	2.0 / 0.9	norm.	+	15	15 / no	yes	a) + / b) +++ / ++	a) 2.6I / b) 1.0I	—	a) — / b) 9.8	a) — / b)4.3 / 3.7	yes / mild	a) hemosid. / b) extens. cirrhosis, focal necrosis	died; intest. obst. peritonit., hepat. fail.	70 Tr. in 16 mos.

* Hepatic enlargement, if present, greater than 3 cm.
** *a*) and *b*) indicate separate admissions.
† D = direct; I = indirect.
¶ Prothrombin time: Normal = 14 seconds ± 2 seconds.
§ Alkaline phosphatase: Normal = 2.5 to 4.0 Bodansky units.
†† Normal albumin = 4.0 to 4.7 gm.; globulin = 2.0 to 2.7 gm.

TABLE 2 (A).—CASES OF HEMOLYTIC ANEMIA ASSOCIATED WITH ABNORMAL LIVER FUNCTION

	Name Sex	Age	Hgb. (gm.) / RBC × 10⁶ (lowest)	RBC fragil.	Coombs test	Nucl. RBC/100 WBC	Retics. % / Spherocytes	Liver enlargement*	Ceph. / Thymol.**	Bilirubin†	Prothromb. time (secs.)¶	Alk. phosphatase§	Alb. / Glob. (gm.)††	Splenectomy / response	Liver biopsy	Follow-up	Notes; No. of transfusions (Tr.)
1)	M. C. F	30	3.0 / 1.0	incr.	+	3	20 / yes	yes	++++ / ++++	2.5I	—	3.5	3.5 / 2.8	yes / slight	cirrhosis, periport. necrosis	died; anemia, cardiac fail.	20 Tr. in 2 mos.
2)	M. S. F	10	2.0 / 0.9	norm.	+	15	15 / no	yes	a) + / b) +++ / ++	a) 2.6I / b) 1.0I	—	a) — / b) 9.8	a) — / b)4.3 / 3.7	yes / mild	a) hemosid. / b) extens. cirrhosis, focal necrosis	died; intest. obst. peritonit., hepat. fail.	70 Tr. in 16 mos.

TABLE 2 (A).—CASES OF HEMOLYTIC ANEMIA ASSOCIATED WITH ABNORMAL LIVER FUNCTION

	Name / Sex	Age	Hgb. (gm.) / RBC × 10⁶ (lowest)	RBC fragil.	Coombs test	Nucl. RBC/100 WBC	Retics. (%) / Spherocytes	Liver enlargement*	Ceph. / Thymol.	Bilirubin†	Prothromb. time (secs.)¶	Alk. phosphatase§	Alb. / Glob. (gm.)††	Splenectomy response	Liver biopsy	Follow-up	Notes; No. of transfusions (Tr.)
9)	B. L. M	7	9.9 / 3.5	incr.	—	0	5 / no	yes	+++ / +++	1.8I		1.7	3.6 / 3.4	no	—	Condition fair	Hippuric excretion 40% normal
10)	C. L. F	17	2.5 / 1.3	incr.	0	6	31 / no	no	+++ / +++	1.0I	21.6	2.5	4.6 / 2.3	no	—	Spont. remission	Well 7 yrs., incr. fragil. persists
11)	E. W. F	79	5.1 / 1.0	—	—	12	35 / yes	?	++++	25.0D	25.5	4.8	4.2 / 2.3	no	—	Unknown	
12)	C. E. W. M	37	6.0 / 1.9	norm.	0	0	18 / no	no	++++ / ++	2.0I		3.0	4.5 / 2.9	yes / good	hemosid., periportal round cell infiltr.	Good, short term	Hepatitis subsided; BSP 41% after 30 min.; 7 Tr.
13)	J. H. F	1	4.0 / 1.8	norm.	++++	79	67 / no	yes	+++ / 0	2.2I	21.7		5.2 / 2.9	yes / none	a) hemosid., toxic hepatit. b) fibrosis also	Died; anemia, cholemia	43 Tr.
14)	R. T. F	23	10 / 2.9	norm.	+++	0	6 / no	yes	++++ / +++	3.4I		2.4	4.6 / 3.4	no	—	Anemia in remission, hepat. dysfunction persists	BSP 10% after 30 min.; no Tr.
15)	C. P. F	34	7.6 / 2.3	norm.	—	0	12 / no	yes	++++ / —	6 I		2.1	4.2 / 2.7	no	—	Fair	BSP 20% after 30 min.
16)	J. M. M	61	4.0 / 1.3	—	—	1	5 / no	yes	++ / —	3.2I		5.0	3.3 / 1.7	no	Hemosid., congest., bile plugs	Died: pulm artery thrombosis, aplasia	BSP 18% after 30 min.; 36 Tr. in 6 wks.
17)	F. R. M	59	7.8 / 2.3	incr.	0	0	29 / no	yes	++ / +++	2.6I	15.3	5.4	5.1 / 1.8	no		Unknown	
18)	A. M. M	53	7 / 4.2	incr.	0	4	7 / no	yes	+++ / +++	1.1I	13.0	4.7	3.9 / 4.0	yes / none	Hemosid., mild fibrosis	Anemia; liver dis. active	BSP 40% after 30 min.

2 B).—CASES OF SYSTEMIC DISEASE WITH LIVER INVOLVEMENT AND SYMPTOMATIC HEMOLYTIC ANEMIA

19)	M. J. F	65	6.5 / 2.0	incr.	0	0	17 / no	yes	++++ / —	1.4I	14.5	4.7	4.3 / 2.8	yes / none	Lymphosarcoma; hemosid.	Unchanged, receiving radiotherapy	
20)	H. L. F	45	5.3 / 1.8	norm.	—	3	20 / no	yes	+++ / —	1 I		7.1	3.3 / 2.2	yes / fair	Boeck's sarcoid	Good	
21)	E. F. F	26	9.6 / 3.4	incr.	—	0	4 / no	yes	—	1.5I		9.5	4.2 / 2.9	yes / none	Gaucher's dis.	Fair	

blowing, apical, systolic murmur. The spleen was moderately enlarged but the liver was not palpable. Abnormal laboratory findings consisted of a hemoglobin of 4.8. gm., a red blood cell count of 1,000,000 with 18% spherocytes, 70% reticulocytes, and 17 nucleated red cells per 100 white cells. Red cell fragility was considerably increased. The cephalin flocculation was +++, bilirubin 5.1 mg. indirect, urine urobilinogen increased, and there was bromsulfalein retention of 25% after 30 minutes.

Following 4 transfusions, splenectomy was performed and a 2 kg. spleen was removed with histologic findings consistent with the diagnosis of hemolytic jaundice. The liver was greatly enlarged, and appeared cirrhotic with a thickened capsule. On biopsy, diffuse swelling of liver cells was noted. Gallstones were palpated. Postoperatively only mild symptomatic improvement occurred.

Her final admission was in 1949, 4 years later, occasioned by progressively deepening jaundice, pruritus, recurrent epistaxis and increasing hepatomegaly. Her hemogram continued to reveal a severe macrocytic anemia. The only significant laboratory changes consisted of a +++ positive Coombs test, ++++ thymol turbidity (cephalin flocculation remained +++), serum globulin 3.7 gm., albumin 3.1 gm., prothrombin time 30% of normal, bromsulfalein retention of 35% after 30 minutes, and a reversal of the cholesterol partition. She was discharged to a nursing home on a high-protein, high-caloric diet with the diagnosis of coarse nodular cirrhosis and acquired hemolytic anemia. She died at home 2 months later, with hematemesis and deep jaundice. No postmortem examination was made.

Case 3. W. R., a 17-year old girl, was first seen at Presbyterian Hospital in 1948 with a 5-year history of non-pruritic jaundice, intermittently dark urine, easy bruisability and bleeding gums. Splenomegaly had been noted 3 years before admission and a macrocytic anemia 1 year previously. There was no family history of jaundice or anemia. Deep icterus, marked splenomegaly and dilated abdominal veins were noted. A moderate macrocytic anemia was present with a hemoglobin of 9.5 gm., and 8.6% reticulocytes. The white cell count was 1200, with a normal differential, the platelet count was 55,000. The cephalin flocculation and thymol turbidity tests were ++++, serum albumin 3.0 gm., globulin 2.9 gm., bilirubin 2.3 mg., and urine urobilinogen increased.

A splenectomy was performed by Dr. A. H. Blakemore and a splenorenal shunt constructed. The spleen weighed 5100 gm. and was found to show thickening of the trabeculae and blood vessels. The liver was shrunken, firm and nodular and revealed cirrhosis and periportal necrosis histologically. The patient did well postoperatively and in addition to subjective improvement there was considerable improvement in liver chemistries and a return of the hemogram almost to normal, possibly secondary to relief of hypersplenism.

Fifteen months later she was readmitted for typhoid fever with positive blood and stool cultures. Five days after termination of a successful course of therapy with chloromycetin, a hemolytic crisis suddenly supervened with a temperature spike to 103°F, progressive fall in the hemoglobin level to 6.5 gm. and red blood cell count to 2,000,000. A reticulocytosis of 19% developed, 200 nucleated red cells per 100 white cells appeared in the peripheral blood, white cell count rose to 27,000, urine urobilinogen and serum bilirubin became mildly elevated and a moderate increase in red cell fragility was noted. The Coombs test remained negative. Spontaneous recovery occurred with a return to an essentially normal hemogram in 3 weeks. Moderate abnormality of liver function tests persisted and the patient was discharged with the diagnosis of coarse nodular cirrhosis and an episode of acquired hemolytic anemia.

Increased red cell fragility persists. It seems unlikely that chloromycetin acted as an hemolytic agent, since it had been discontinued 5 days prior to the acute hemolytic episode and since reintroduction of chloromycetin therapy had no untoward effect. In addition, no toxicity of this sort has been ascribed to the drug to date.

Discussion. In addition to the 3 patients described above, a search of the Presbyterian Hospital records since 1932 has revealed 18 additional cases exhibiting well-defined acquired hemolytic anemia associated with derangement of the liver. Details of all 21 cases are given in Tables 1 and 2. It will be noted that the first 8 patients described in Table 1 were proven by liver biopsy to have damaged livers. In general, their liver function determinations gave evidence of marked hepatic dysfunction. Thirteen additional patients,

TABLE 3.—CASES OF ASSOCIATED LIVER DISEASE AND HEMOLYTIC ANEMIA FROM THE LITERATURE

Case	Lowest Hgb. (gm.) or % / RBC × 10^6	RBC fragil.	Coombs test	Nucl. RBC/100 WBC	Retics. (%) / Spherocytes	Liver enlargement*	Ceph. / Thymol	Bilirub. (indirect)	Splenectomy response	Liver biopsy	Follow-up	Notes
Van den Bergh and Kammerling[20] (1935)	6 gm. / 2.1	norm.	—	present	14 / no	yes	—	"33 u"	no	Laennec's cirrhosis	Died	Galactose retention present
Davidson[4] No. 5 (1938)	18% / 0.7	incr.	—	present	42 / yes	yes	—	100 (Jet. Index: Biphas.	no	Portal cirrhosis	Died	?agglutinins; (marked clumping of erythrocytes)
Watson[21] No. 71 (1937)	65% / 2.8	—	—	—	15 / —	yes	—	179 (Jet. Index: Biphas.	no	—	Improved spont.	Urobilinogen of stool & urine marked. incr.
Lovibond[12] (1938)	22% / 1.35	norm.	—	present	77 / no	yes	—	4 u	no	Ac. yellow atrophy; splen. congest.	Died in 6 wks. after Tr.	
Farrar,[8] Burnett and Steigman (1940)	5.8 gm. / 2.4	norm.	Circul. hemolysin	6	4 / no	yes	—	7.5	yes / good	Fatty cirrhosis	Full response 11 wks. after splenectomy	
Stacy[18] (1946)	5.4 gm. / 1.7	norm.	Circul. hemolysin	4	15 / no	yes	—	1	no	Fatty cirrhosis, hemosid.	Died 4 months after adm.	

* Hepatic enlargement, if present, greater than 3 cm.

while showing equally severe hemolytic anemia, either lacked liver biopsies or appeared both from chemical and histological tests to have lesser degrees of hepatic damage. In some of them the liver dysfunction may represent a functional rather than an organic derangement (see Table 2A). The difficulty of making this distinction without liver biopsy in the presence of severe hemolytic anemia is exemplified by Patients C. L. and C. E. W., in whom the hepatic disease may well have been transient infectious hepatitis. Finally, 3 cases are summarized in Table 2B with coexisting hemolytic anemia and liver disease, but which eventually were proven by liver biopsy to have a systemic disease. Here the anemia could probably be classified as a "symptomatic hemolytic anemia". This total series has been tabulated because of the possibility that milder or earlier forms of a common pathological process might otherwise be omitted.

A search of the literature has uncovered a number of similar cases of hemolytic anemia in association with liver disease. Table 3 lists those in which adequate data are given to justify inclusion.

For purposes of analysis it seems best to confine our attention largely to the first 8 proven cases in Table 1. In 3 of them, it is impossible to determine definitely whether the anemia or the liver disease appeared first. But Case W. R. demonstrates that the acute hemolytic process may occur 15 months after the histological demonstration of cirrhosis and after the spleen has been removed. In one case (J.B.) it is probable that serum hepatitis occurred as a pre-terminal event, but significant liver damage was present previously. In no other instance could liver disease be linked to a transfusion given for anemia.

Types of liver disease represented in the 8 cases consist of cirrhosis either histologically or grossly, or both, in 4, clinically compatible with coarse nodular cirrhosis; and focal necrosis and hemosiderosis in 4, with the addition of "fibrosis" in 1 case. There was no history of significant alcohol intake in any instance, and the possibility exists that all cases represented cirrhosis following chronic hepatitis.

Coombs tests were performed in 5 of the first 8 cases. Three were +++ to ++++, 1 was weakly positive, and 1 was negative. Red cells coated with a demonstrable antigen were therefore often but not invariably present. It is of interest that of 4 cases with spherocytosis, 3 had positive Coombs tests and they all probably represent acquired hemolytic anemia[17].

More than 4 transfusions had been given to 4 of the first 8 cases prior to histological study of the liver. In these instances hepatic hemosiderosis may have been in part due to the blood administered. However, the duration of the disease was not that usually required for the development of exogenous hemochromatosis[15] due to transfusions, and in only 1 case (M.S.) did the number of transfusions seem sufficient to induce this process.

Marked hepatic enlargement was found in 7 of the first 8 cases and marked splenomegaly existed at one time or another in all 8. Comparison of the 75% mortality in this group with the 15% figure for the remaining 13 cases indicates that the severity of the liver disease appears to be outstanding in determining the prognosis. Six of the first 8 cases underwent splenectomy. The characteristic pathological report was congestion of the sinusoids and thickening of the septa, at times accompanied by hemosiderosis and foci of extramedullary hematopoiesis. In only 2 of the 6 cases that underwent splenectomy was there slight subsequent decrease in the hemolysis, and in both of these it proved transient. Among the 13 milder and less definite cases, 6 additional splenectomies were

done, and the only one appearing to have a really satisfactory response (C.E.W.) had but mild hepatic damage at the time of operation, and so far has had only a brief follow-up. The general failure of splenectomy in the group of patients with hemolytic anemia in association with liver disease is disappointing and is in contrast with the better results secured in acquired hemolytic anemia without liver disease.

Speculation on the mechanism underlying the association of hemolytic anemia and severe liver disease has borne little fruit to date. It might be postulated that the liver may be damaged in such a way that its normal capacity to degrade or detoxify hemolytic factors produced in the body may be impaired. Excessive hemolysis might then result, and its products, by placing a further load on hepatic function, might aggravate the liver damage. Hoet[12] and Heinle *et al.*[11] offer some experimental evidence in this regard. Hemolytic factors may be elaborated by the spleen and general reticulo-endothelial system, and with the hypertrophy of these tissues frequently associated with liver disease, could well be produced in excess. The generally disappointing results of splenectomy, however, indicate that excess production of hemolysins by the spleen is not an important factor. It is equally possible that some abnormal metabolite secondary to liver injury, acting as an antigen, might cause the production of abnormal antibodies which were responsible for red cell destruction. The evidence that cortisone inhibits antibody production as demonstrated by Bjorneboe *et al.*[10], combined with the apparent response to cortisone in the first case described, and the not infrequent occurrence of a positive Coombs test, suggest that an antigen-antibody reaction may be involved. Furthermore, undetected low-grade hemolysis may occur regularly in association with the B_{12}-resistant, macrocytic anemia of liver disease, and this series may merely represent the more severe, clinically apparent cases. This question is being subjected to experimental study.

Summary. Eight cases of histologically proven liver disease in association with marked hemolytic anemia occurring in a single hospital during a span of 17 years have been analyzed and 3 cases described in detail. Thirteen additional instances of similar anemia with milder and less definite hepatic dysfunction have been tabulated. Comparable cases have been secured from the literature.

Six of the 8 severe cases underwent splenectomy, and in none was there a significant response, though in 2 there may have been slight benefit. This is in sharp contrast to the more favorable results often obtained after splenectomy in acquired hemolytic anemia without liver disease. In one patient a remission of the anemia occurred on 2 occasions following the administration of cortisone.

The most important prognostic factor appears to be the severity of the liver disease, since 6 of the 8 deaths occurred among the 8 cases with the most marked hepatic disturbance.

Gross and histopathologic study of the liver was possible in 13 cases. Of the 8 cases with most marked damage, the picture was that of cirrhosis in 4, and of focal necrosis with hemosiderosis in the remainder. It is possible that all of these represented the sequelae of a chronic hepatitis of virus origin. In 3 instances, liver biopsy revealed a systemic disease (lymphosarcoma, Boeck's sarcoid, and Gaucher's disease) so that the hemolytic anemia could be classified as symptomatic.

Although the association of acquired hemolytic anemia and hepatic disease is stressed, no satisfactory explanation is available as to how one may predispose the patient to the other.

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PROGRESS
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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THE TEMPOROMANDIBULAR ARTICULATION SYNDROME

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DISTURBANCES involving the temporomandibular articulation have long been known to exist, but are more frequently overlooked than recognized. Too many cases have been incorrectly diagnosed as atypical trigeminal neuralgia, avitaminosis, catarrhal otitis media, and non-specific parotitis. Unfortunately, paranasal sinuses have been operated upon, tympanic membranes have been incised, and the trigeminal nerve branches injected with alcohol, all in a vain attempt to relieve the symptoms of distress associated with the temporomandibular joint.

Reisner[13], Bauer[2], Costen[6], Axhausen[1], and others[3,5,7-17] have, through extensive investigation, pointed out the various mechanical and pathological factors concerned in this very disturbing syndrome.

In order fully to comprehend the pathology of the temporomandibular joint it is essential to understand the normal articulation and occlusion.

Anatomy. When considering symptoms referable to this joint, one must bear in mind that it is very complicated, being neither a true ginglymoid or hinge joint nor an arthrodial or gliding joint, but rather a combination of the two. As succinctly stated by Thoma[17], "it is capable of hingelike rotary motion, gliding anteroposterior motion and a slight amount of vertical motion; by alternate action of the homologous joints it allows lateral motion, and by a combination of all these, circumduction." This compound joint is formed chiefly by the anterior root of the zygomatic process of the temporal bone (which forms the mandibular fossa) and the articular eminence above, and the condylar process of the mandible below, both separated by a cartilaginous meniscus or disc. This disc is molded between the two surfaces, thus compensating for the variation between the articulating surfaces of both bones. It thus divides the entire joint space into a meniscotemporal articulation above and a meniscocondylar articulation below, both of which are thoroughly enclosed by a completely investing capsule. The mandibular fossa and the articular

tubercle are covered with a thin layer of cartilage to permit the easy movement of the meniscus. The primary structures that hold the jaw firmly within the joint cavity are the stylomandibular, sphenomandibular, and the capsular or temporomandibular ligaments.

There are two types of temporomandibular fossae, mainly emphasizing the depth of the joint cavity, and sometimes referred to as the open and closed forms. The former is understandably shallower than the latter and is found mostly in individuals that emphasize gliding movements of their jaws. The closed form is deeper and is seen more commonly in those individuals that emphasize the hinge function of the jaw.

The cartilaginous meniscus of the temporomandibular articulation is a most important component in disturbances of this joint. The presence of teeth in both upper and lower jaws, especially the posterior ones, acts as a counterbalance for the joint, relieving pressure on the disc from the head of the condyle. The teeth, however, must be in a normal relationship from the standpoint of vertical dimension. When the teeth are in normal occlusion, the anterior surface of the upper part of the head of the condyle is in relationship with the posterior surface of the articular eminence. It is obvious, then, that disturbance of this relationship or loss of teeth may produce varying degrees of pressure on the meniscus, even to the point of complete destruction.

In a normal bite there is a definite convex curve of compensation at the plane of occlusion. When the occlusion reveals an edge-to-edge relationship of the anterior teeth, instead of the mild normal overbite, the occlusal plane becomes straight and encourages lateral excursions more easily. These movements are primarily the function of the external pterygoid muscles. The upper head of this muscle originates in the sphenoid and inserts in the head of the condyle at the margin of the disc. The lower head arises from the lateral pterygoid plate and is inserted in the neck of the condyle, rather than the head. Normally, the upper head draws the disc forward and initiates the gliding motion, while the lower portion rotates the head of the condyle. In the type of occlusion under discussion, the upper portion of the external pterygoid increases in size, because its function becomes primarily concerned with the lateral movements in a horizontal direction.

In the extreme overbite the incisal edges of the lower teeth touch the lingual portion of the upper teeth or even the gingivae, and the compensating curve is further disturbed. In this group the lower head of the external pterygoid muscle is predominant, because it is chiefly concerned with the lateral movements in a vertical direction, tilting the condylar head forward and producing firm compression on the meniscus.

The elevators of the mandible include the powerful masseter, temporal, and internal pterygoid muscles and the less powerful external pterygoid muscle. The depressors of the lower jaw include the digastric, platysma, geniohyoid, geniohyoglossus, and mylohyoid muscles. With such powerful elevators of the jaw, it becomes obvious that the extent of closure must of necessity be limited by the teeth. Since most of the power of the masticatory muscles is applied posteriorly, it becomes obvious also that the posterior teeth are the site of chewing. With the loss of these teeth the mandibular joint assumes an increased amount of trauma and possible structural damage, even to the point of destruction of one or more of the component parts.

Symptoms. Auditory disturbances are among the most common in the

temporomandibular syndrome. The ear symptoms may be intermittent but sometimes are continuous and include impairment of hearing, dull or aching pain, tinnitus, and the stopped-up or stuffy sensation during mastication. Extraoral symptoms include vertical, occipital, or postauricular headaches, snapping, or clicking noise in front of the ear when opening or closing the mouth, burning sensation in the throat, and sometimes a dryness in the mouth. In the experience of the author the clicking or snapping noise and burning sensation in the mouth or throat are the two most frequent complaints.

Headaches and pain are two of the most distressing symptoms. In cases due to malocclusion the pressure of the condyle is applied too far posteriorly, and the constant pounding of the condyle in this abnormal position produces a pressure atrophy in the posterior part of the glenoid fossa and a flattening of the posterior portion of the articulating surface of the head of the condyle. As the bone atrophy in the glenoid fossa increases, the auriculotemporal nerve, which passes through the posterior part of the joint, becomes injured by the condylar head of the mandible with a resulting neuralgia. When the chorda tympani, which passes through the mesial edge of the joint, becomes irritated or injured, burning, persistent pain in the tongue is a most distressing complaint.

Catarrhal otitis media associated with temporomandibular joint disturbances is usually due to compression of the eustachian tube. Tinnitus and vertigo as a rule are due to changes in intratympanic pressure, producing a change in the labyrinth. This is relieved by inflation.

When the snapping or clicking noise occurs at the opening movement of the jaw, it is usually due to a thickening of the meniscus and impaction of the disc during articular activity. When the clicking noise is heard midway between the closed and opened position, the disc is pushed forward because the condyle in the fossa is displaced upwards.

When ear symptoms are produced by temporomandibular joint lesions, there is usually found a disturbance of the dental occlusion in its vertical dimensions. Correction of this relationship will very frequently cause a cessation of the ear difficulties.

The occurrence of acute infectious or pyogenic arthritis is not very common, but when it does occur, it must be dealt with properly, else the complications that may result will end in facial deformities. This type of involvement is more commonly seen in children as a complication or sequel to one of the exanthemata, particularly scarlet fever, although it is not infrequent in adults also. It has at times been incorrectly diagnosed as mumps, parotid abscess, and hysteria, and at other times has been totally ignored. At the onset the patient usually complains of severe pain in front of the ear radiating upward to the temple and downward to the angle of the mandible. There is also a very acute pain on opening or closing the mouth. If the condition is untreated, ankylosis may result, and if this occurs in childhood, then there is lack of development of the mandible with its resulting typical deformity, sometimes referred to as "squirrel face." Dental hygiene is neglected and teeth are lost. This latter adds to the maldevelopment or underdevelopment of the mandible. Strangely enough, these patients manage to obtain sufficient nourishment for their needs.

Roentgenograms are always taken with the mouth open and closed; the normal joint is taken for comparison with the involved joint. The findings vary in degree with the underlying

pathology but there is usually seen a narrowing of the joint space, a disturbance in the degree of excursion of the head of the condyle.

Treatment. The treatment of the acute stage consists primarily in putting the jaw at rest, either by orthodontic appliances, intermaxillary, or by modified wiring of the jaw; the application of heat; salicylates for pain; and one of the antibiotics in adequate dosage. If, however, ankylosis results, it comes on gradually over a prolonged period of time. Much can be done before the process becomes complete. Adhesions can be broken up in the joint by means of the Ivy[8] dilator, using increasing amount of pressure until adequate opening is obtained and maintained. When, however, the process becomes fixed, then arthroplasty is the procedure of choice.

The chronic type of arthritis is more commonly seen in adults, and, although it may rarely be due to gout, rheumatism, or gonorrhea, the most frequent cause is chronic trauma. In his excellent monograph on the basis of extensive microscopic investigation, Bauer[2] has classified all chronic non-infectious proliferative inflammatory changes in the temporomandibular joint as osteoarthritis deformans. This is commonly due to a change in the normal vertical relationship of the dental occlusion, such as loss of teeth, or recurring luxation or subluxation due to loss of tonicity of the articular ligaments. In such instances the head of the condyle leaves the glenoid fossa on opening the mouth and assumes a position beyond the articular eminence. As the mouth is closed, the powerful elevators of the jaw come into play and pound the head of the condyle with force against the remaining articular components. In addition to the chronic inflammatory changes, there is an internal derangement of the fibrocartilaginous disc, with varying degrees of destruction. In these cases the most disturbing symptoms are pain in the joint region and a loud clicking noise heard in front of the ear.

The treatment depends upon the amount of intra-articular damage. Conservative measures, however, should be given a fair trial before any surgical procedures are instituted. It is advisable to construct an orthodontic appliance consisting of two bands with lugs, in each quadrant; these bands are connected by a rod soldered to them and then the entire appliance is cemented to the teeth. Small intermaxillary rubber bands are applied in an attempt to limit the motion of the jaw. These rubber bands also supplement the weakened periarticular ligaments. With the traction applied it is obvious that the head of the condyle is limited in its sphere of excursion, and consequently the amount of pounding is decreased. Physiotherapy in the form of heat and massage daily is important. This treatment should extend over a period of 3 to 6 months. The Writer has seen many excellent results with this procedure. When, however, intra-articular damage has been beyond the means of such therapy, then meniscectomy must be considered.

Turner and Clarke[18] have described a most interesting clinical picture of temporomandibular arthropathy in serum sickness. Such cases are undoubtedly frequently overlooked or mistaken, in accident cases, for tetanus and its associated muscular trismus.

Summary. The temporomandibular joint may become involved in a symptom complex that is based 1) primarily on a disturbance of mechanical factors producing a definite pathological entity of a traumatic nature, or 2) primarily on disease of an inflammatory or bacterial nature. An attempt is made to analyze the disturbance of the normal mechanical structure and construction of the joint and point out the manner

in which symptoms are produced. It is an established fact that variations from the normal functioning mechanism may produce most annoying and distressing symptoms. If the damage to the component parts of this joint have not progressed too far, then relief may be obtained by adjustment of the vertical dimension of the dental occlusion. When the lesion is of an inflammatory or bacterial nature, then the principles of treatment are the same as those applicable to similar lesions in other joints.

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DERMATOLOGY AND SYPHILOLOGY

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SOME ASPECTS OF BERYLLIOSIS

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IN 1943 Van Ordstrand and his colleagues[74] described a chemical pneumonitis in workers extracting beryllium oxide from ore. This aroused a great deal of study of the hazards that may be incident to the extraction, processing and handling of beryllium and its compounds. More recently, because of the wide use of fluorescent lamps, there has been observed an increasing number of cutaneous lesions that have been traced to accidental implantation of beryllium compounds into wounds and cuts. Although prophylactic measures have reduced the dangers of systemic involvement, and the use of beryllium in fluorescent lights has been outlawed[39], the effects of beryllium preparations on man and animals are of great interest because of the light they may throw on the problem of sarcoidosis. In this presentation we propose to outline briefly the clinical syndrome produced by beryllium compounds, to compare it with sarcoidosis, and to discuss the possible pathogenesis of the beryllium symptoms.

BERYLLIUM AND ITS USES. Beryllium and its toxicology are fully discussed in the Leroy V. Gardner Memorial Volume on pneumoconiosis[78], in Hamilton and Hardy's Toxicology[32], in Morgis and Forbes'[52a] review of the literature and in the 1943 monograph of Hyslop and co-workers[38]. By 1943 a certain amount of literature had already been accumulated on "beryllium poisoning", "berylliosis", and "beryllium rickets".

Beryllium is a rare metallic element that is found in nature chiefly as beryl. It contains 14% beryllium oxide. Its atomic weight is 9.02, and it belongs to the calcium, magnesium and barium group in the periodic system of elements.

It is part of fatigue-resistant copper alloys as well as alloys of aluminum and nickel; as a phosphor in fluorescent lamps and in certain Roentgen-ray apparatus (filters and beryllium glass tubes) and radio tubes. Its chief usefulness however, is in the fatigue-resistant beryllium copper alloy.

CLINICAL ASPECTS OF BERYLLIOSIS. Although evidence of beryllium effects of several types, including cutaneous, had been known for some time (see Hyslop *et al.*[38]) it was not until 1943, when Van Ordstrand[74] described a beryllium pneumonitis, that the basis of our present knowledge of the effects of beryllium on human tissues was laid. Two types of pneumonitis (Dutra, with others, believes that they are merely phases of the same, incident to such differences as solubility) have been described: an acute form, which in general has been associated with the extraction of beryllium from ore, and a chronic granulomatous form (described by Hardy and Tabershaw[35] and by Higgins[37]), which has been referred to as miliary sarcoidosis, chronic granulomatous pneumonitis, delayed chemical pneumonitis, and beryllium sarcoid. This latter form has in general been associated with fluorescent phosphors containing beryllium. Both forms, however, are not invariably associated with a particular beryllium compound, for the acute form of pneumonitis has been seen in individuals in contact with beryllium phosphor and the chronic type has been observed subsequent to exposure to beryllium oxide.

Although a number of authors have reported cases of pulmonary beryllosis[1,3,5,6,9,11,12,13,14,16,25,31,33,34,49,50,57,59,62,64,68,74,75,76,77,79,80,81], an idea of the symptomatology may be obtained from the report of De Nardi, Van Ordstrand and Carmody[13], who reviewed 406 cases of acute dermatitis and pneumonitis in an 8-year period. According to these investigators, in the acute or fulminating type, which is least common, the symptoms may appear within a few hours or as late as 72 hours after exposure to anhydrous beryllium sulfate fumes. The patient complains of spasmodic cough, tightness of the chest, with substernal pain, severe exertional dyspnea and, in the severe cases, variable degrees of cyanosis. Physically the patient presents acrocyanosis, sudden decrease in vital capacity of the lungs, and rales throughout the chest. Recovery is rapid. In the chronic type, which follows prolonged exposure to the fumes or dusts of such beryllium compounds as the sulfate, tetrahydrate, fluoride and oxide, the symptoms may occur years after exposure. The most frequent subjective complaints are dyspnea on mild exertion, spasmodic cough aggravated by a supine position (sputum rarely blood streaked), substernal burning pressure or pain noted especially on inspiration, general weakness and anorexia with weight loss, in amount depending on the duration of the disease before treatment. It might be noted parenthetically that Chesner[6] re-emphasizes the occurrence of chronic pulmonary disease of high fatality in persons living in a community where beryllium is processed.

The roentgenographically visible changes in the lungs are described by Sosman and Wilson in the Hardy and Tabershaw report[35] as occurring in 3 stages:

"1) *Stage of Granularity.* This is the most distinctive stage and there is no other disease which even closely mimics the appearance of the lungs in this stage. Small, finely particulate granulations are seen diffusely throughout each lung field. These have the appearance of fine sandpaper; and when seen under a magnifying glass resemble a 'sandstorm'.

"2) *Stage of Reticulation.* In this stage a reticular pattern is superimposed on the granular background. There may be slight fuzziness and enlargement of the hilar areas.

"3) *Stage of Nodulations.* This is the phase which is most likely to be confused with other diseases; for this stage closely mimics sarcoidosis, car-

cinomatosis, erythema nodosum and miliary tuberculosis.

"In this stage there are distinct nodulations up to 5 millimeters in size which do not calcify, cavitate or coalesce and create the appearance of a 'snowstorm'. The hilar areas may appear even more fuzzy and prominent. Prominent cor pulmonale with right-sided cardiac enlargements may be noted in this stage."

Hardy also noted, in a later series[34], emphysematous changes at the apices, frequent mid-zonal distribution of density, and 4 instances of spontaneous pneumothorax. Maitland and his co-workers[50] observe:

"Although this is a convenient classification, it has been noted that the most severe type of pulmonary crippling with extreme fibrosis, marked pulmonary hypertension with cor pulmonale and right-sided cardiac enlargement may occur with the chest film findings typical of the stage of reticulation. Conversely, individuals who have chest films typical of the stage of nodulations may be far less crippled. Consequently, the contour of the heart (cor pulmonale, right-sided enlargement) is a good index of the degrees of pulmonale crippling present. Areas of compensatory emphysema may be noted in most cases. Spontaneous pneumothorax, however, is unusual."

The cutaneous lesions of berylliosis have also been the subject of intensive study[7,17,25,29,54,55,69,70]. Grier, Nash and Freiman[29] classified the cutaneous lesions that have been observed among those who come in contact with beryllium compounds as follows:

1. Contact dermatitis.
2. Skin ulcer.
3. Lesions arising spontaneously in patients with the chronic type of lung disease (pulmonary granulomatosis).
4. Subcutaneous granuloma occurring in persons who cut themselves on fluorescent lamps.

Contact dermatitis occurs in persons working with soluble salts of beryllium (beryllium fluoride or beryllium sulfate); the ulcers result when crystals of soluble beryllium salts are embedded in the tissues; the granulomas of the skin in some patients suffering from chronic pulmonary berylliosis are similar in structure to the lung lesions.

Fortunately, with the outlawing of the use of beryllium in fluorescent lamps, the fourth type of lesion, first described by Grier and his co-workers[29], should all but disappear. This type, which is in reality distinctive and which has the same pathologic structure as the pulmonary lesions also, brings up the question of the objective distinction of beryllium lesions from sarcoidosis.

Other findings in various systems and organs have been described. Some of these will be mentioned in the comparison of sarcoidosis with berylliosis.

Numerous recent compilations on sarcoidosis[8,10,26,28,47,48,51,52,53,58,61,63,65,73], especially that of Freiman[22] who also studied berylliosis, yield much information on the clinical involvement by sarcoidosis which may be compared with those in berylliosis. Enlargement of lymph nodes has been observed in both processes[34,59]. The pulmonary findings produced by beryllium have been misdiagnosed as sarcoidosis. The heart is involved in both processes[34,59]; kidney dysfunction has been observed in beryllium disease by Pyre and Oatway[59]. Roentgenograms or clinical observations do not reveal the presence of osseous changes so characteristic of sarcoidosis, but Dutra and Largent[18] have produced osteogenic sarcoma in rabbits by serial intravenous injections of beryllium oxide or a phosphor containing beryllium oxide. (Cf. Barnes

et al.[3a]) No apparent ocular or lacrimal or salivary gland involvement, such as is seen in sarcoidosis, has been reported in berylliosis, although acute nasal and pharyngeal and bronchial mucosal involvement does occur[64]. No outstanding gastrointestinal, endocrine and nervous symptoms, such as may occasionally occur in sarcoidosis, have been found in berylliosis. The blood findings are, however, of some interest. Although there are no marked changes in the cytology of the blood in beryllium disease (occasional polycythemia[3,34]), the chemical findings show changes somewhat similar to those in sarcoidosis; in berylliosis there is sometimes slightly elevated blood globulin[34] (in sarcoidosis, the total serum protein is elevated but chiefly in the gamma globulin fraction and the A/G ratio is reversed); serum calcium is increased in both; serum alkaline phosphatase is slightly elevated in both[34]; cholesterol values are normal, and serologic tests for syphilis are negative in both (except for so-called syphilitic sarcoidosis[4,21]). The tuberculin test is negative in both[59], but this as well as the Kveim test and the BCG test has not apparently been studied specifically in beryllium disease.

Both diseases may have a prolonged low-grade chronic course, although fever is not a prominent feature of beryllium disease[3]. In both diseases, pulmonary fibrosis may lead to fatal outcomes.

In regard to the histologic picture, sarcoidosis is characterized by a monotonous uniformity[52]; it consists of tuberculoid accumulations of epithelial cells with only a thin, or no, mantle of lymphocytes. Within the epithelioid zone there may be an occasional Langhans' giant cell. Necrosis and caseation are relatively minor. The tubercles are isolated in an alveolated arrangement by fibrous tissue bands. Healing is said to occur by fibrosis. Inclusion bodies are of 3 types[22,72]; spiculated body or asteroid forms may occur in about 6% of cases of berylliosis but in 30% of cases of sarcoidosis[22,47]. The asteroid bodies, however, have been observed in a variety of granulomas, such as tuberculosis, leprosy, histoplasmosis, schistosomiasis, and lipoidal granuloma.

In the few tissues from berylliosis we have studied, the features were similar to those of sarcoidosis. In fact, without clinical data, they were so diagnosed by ourselves and others. Dutra[16], who has described the microscopic features in cases of beryllium pneumonitis, gives data which if closely followed, would serve to differentiate Boeck's sarcoid from beryllium disease. In the chronic form the relative infrequency of epithelioid cells in beryllium disease is in marked contrast to the situation in sarcoidosis. On the other hand, without history or demonstration of beryllium in the tissue, Dutra[17] admits that biopsy of tissue from the skin reveals lesions that could be confused with caseous tuberculosis or Boeck's sarcoid. As special differential points, beryllium lesions are likely to contain caseous areas and large numbers of lymphocytes scattered throughout, especially in the periphery of the lesion. Vorwald and Pratt[78], in the Gardner memorial volume, present a convenient and detailed table on the pathologic features of 4 types of pulmonary disease: pulmonary granulomatosis in beryllium workers, Boeck's sarcoid, silicosis and tuberculosis. These authorities do not offer this differential table as conclusive, but subject to revision as their studies progress. It is interesting in connection with our present discussion that Vorwald and Pratt found sufficient characteristic features histopathologically to differentiate "somewhat similar but otherwise well defined conditions." In the same volume Maitland illustrates

tissue specimens with the pathology "virtually indistinguishable from Boeck's sarcoid." Grier, Nash and Freiman[29] concede that the histology of beryllium granulomas may resemble those of cutaneous and subcutaneous sarcoidosis so closely that, in some instances, the diagnosis of berylliosis may be missed without a history of exposure or determination of beryllium in the tissue. He suggests that usually the beryllium lesions show foci of necrosis of a type not seen in sarcoidosis and the laminated inclusion bodies seem to occur more frequently in sarcoidosis.

In addition to sarcoidosis, differential diagnosis of berylliosis must include other processes such as tuberculosilicosis[57], miliary carcinomatosis, pneumoconiosis, asbestosis[71], coccidioidomycosis, and acute chemical pneumonitis.

The prophylaxis of beryllium disease represents a triumph of modern preventive medicine. Under the able leadership of Dr. James G. Townsend, the Medical Advisory Committee on Beryllium has set up procedures for control against exposure within industry and in public life. The latter was effected by eliminating beryllium from fluorescent lights. The local cutaneous lesion responds to careful excision[17]. For the constitutional type of involvement there is no specific treatment. BAL (2, 3 dimercaptopropanol), benadryl orally and intravenously, aminophyllin, and cough remedies have produced variable grades of relief. Kennedy and his associates[41] administered pituitary adrenocorticotropic hormone (ACTH) to a single patient with apparent improvement, but the follow-up was rather short. According to De Nardi *et al.*[13], the most effective therapy at present depends upon early diagnosis and consists of prescribing minimal exertion so that the patient's reserve is not impaired. Because of decreased vital capacity upper respiratory infections may be serious.

Pathogenesis. In view of the limited number of ways in which a tissue (reticuloendothelial system) may react, it is cause for wonder that the findings in sarcoidosis and berylliosis are as dissimilar as they are. Although in the case of berylliosis, the specific agent producing the pathologic state is known, in sarcoidosis no one etiologic factor has been demonstrated in all cases; therefore, *a priori*, a multiple-factor background for this process must be postulated. In fact, some predisposing background is undoubtedly present in individuals who acquire beryllium disease, for all who are exposed to this element do not develop the disease (hypersensitivity[13]). The "sarcoid" response in tissues, which apparently may vary somewhat depending on the cause eliciting it, is a rather nonspecific reaction. It may be evoked by a variety of causes: silicates[10,23,24]; quartz[19]; trauma[42]; site of previous operation[22]; talcum[30]; lipins from tubercle bacilli; hay and colon bacilli[60]; phosphatides[19,66]; living or dead tubercle bacilli[44]; BCG antigen[15]; Kveim antigen[67]; lepra bacilli[20,43,46]; Leishmaniasis[15]; *Treponema pallidum*[4,21]; fungi, for example, *Histoplasma capsulatum*, animal parasites and viruses, various nonspecific substances, paraffin and other oils[27a,b,40]; certain drugs such as iron, morphine and arsenic[56a,b].

The idea that the tissue changes labeled the so-called sarcoid reaction may be elicited by different antigens as well as by chemically indifferent substances was originally advanced by Volk who believed he had induced a sarcoid structure by means of intracutaneous injection of India ink in a patient with a nodose cutaneous sarcoid, an experience Schaumann and Seeberg[67] could not confirm by the use of ink as well as paraffin injections in patients with lupus vulgaris and sarcoid.

Although the previously mentioned substances and organisms may produce a local lesion resembling sarcoid, we agree with Freiman[22] that since the other features of sarcoidosis have not been associated with the local lesions, there is no justification for considering these instances of sarcoidosis. The wide variety of agents capable of producing such a reaction indicates that they may all have a similar underlying mechanism. This may be the result of a single factor or a combination of factors.

The simplest explanation for the production of the sarcoid reaction by certain of the noxae is that they may be regarded as a localizing agent for an infectious agent which, while gaining access to the focus at a later time, acts as the real and immediate pathogen. If this theory had a proved basis it could explain the fact that only certain exposed individuals develop beryllium disease. In the case of talcum sarcoids Gruenfeld[30] proposes 2 other possibilities: 1) In some, but comparatively few, patients "antibodies" to one of the silicates contained in industrial talcum eventually develop, and 2) the mineral deposits prevent the elimination of bacterial or viral contaminants incident to the surgical exposure. Clinically perceptible inflammations develop when the dormant organisms become virulent.

On the basis of the wide variety of potential causes of the sarcoid response, it is logical to assume that the basic mechanism underlying them is identical. According to Harrell and Fisher[36], Curtis and his group[10,28], and Sabin[66] phospholipids either introduced from without or found at the local site may be the common denominator. Sabin demonstrated that a pure epithelioid cell response may be obtained by intracutaneously injecting guinea pigs with phosphatides obtained from the tubercle bacillus. She believed this response so typical that sarcoidosis could be called a phosphatide disease. Fallon[19] later confirmed this epithelioid response to phospholipids. Ray and Shipman[60] also showed that lipins obtained from the tubercle, hay or colon bacilli produced an epithelioid response when injected into the skin of guinea pigs. Anderson[2] found that the lipoid fractions of tubercle bacilli contained phosphorus and were phosphatides.

Hodge, in discussion of Machle's article in the Gardner memorial volume on pneumoconiosis[78], postulates the need for study of a possible trigger mechanism in the production of beryllium lesions. This concept is so similar to what is here proposed that his suggestion is quoted verbatim:

"The final and seventh item . . . is the study of *the possibility of a trigger mechanism.* This study would be a fundamental one based on the premise that there are probably only a limited number of reactions which the body is capable of undergoing. One would attempt to find out what reaction or reactions it is that beryllium triggers. From the currently recognized responses to beryllium, such as calling forth monocytes, fibrous infiltration, the necrosis in the presence of a high concentration of beryllium, some suggestions as to further experiments may be made. Are these, and other manifestations perhaps now only partially recognized, the visible results of a fundamental derangement occasioned by beryllium?"

As in the case of sarcoidosis, the actual mechanism of beryllium action is unknown. It is obvious that while there now exists no warrant for regarding sarcoidosis and berylliosis as identical, the basic pathogenesis must be closely related. For the present, a *terrain berylliosique* similar to the *terrain sarcoidique* may be postulated to cover our ignorance of the actual process.

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PROCEEDINGS OF

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SESSION OF FEBRUARY 20, 1951

Thromboplastic Potency of Various Morphological Parts of Rabbit Brain. S. GOLLUB, F. E. KAPLAN, and D. R. MERANZE (Research Dept., Mt. Sinai Hospital, Phila.). The thromboplastic potency of the gross morphological parts of rabbits' brains were determined, using a modification of the Quick 1-stage prothrombin determination. Seven preparations of the acetone-insoluble residues representing 7 dozens of brains were tested. The data indicated that the medulla, representing about 12% by weight of such brain powders, clotted normal plasma significantly more slowly than the other brain parts ($p<0.005$). This effect was observed for different concentrations of saline extracts of the dried powders from 0.5 gm. pdr. per 10 cc. to 0.1 gm. per 10 cc. The other brain parts (cerebrum, cerebellum, corpora quadragemini, and cerebral peduncles) gave mean clotting times of 15 seconds for 0.5 gm. per 10 cc. to 21 seconds for 0.1 gm. per 10 cc. Medulla, on the other hand, gave mean clotting times of 21 seconds to 33 seconds for comparable concentrations. Some practical results and theoretical implications of these findings are briefly discussed.

Accelerating Effect of Pyromen in Contrast to Inhibitory Effect of Cortisone on the Arthus Phenomenon in Rabbits. EDWARD G. STUART, M.A., (Dept. of Anatomy, School of Med., Univ. of Penna.). Twenty-four male albino rabbits of approximately 1.5 kg. weight were sensitized with crystalline hen's egg albumin in daily intracutaneous injections containing 0.5 mg./kg. of egg albumin nitrogen. Eight served as controls, 8 received 10 mg. of cortisone daily intramuscularly, and 8 received 10 gamma of pyromen daily intravenously. Treatment continued for 35 days, during which time precipitin tests for serum antibody were made on appropriate days. Seven cortisone-treated animals showed no Arthus reactions, but 1 gave a positive reaction on the 23rd and succeeding days of the experiment. The control animals showed their first Arthus reactions about the 7th day. The reactions became pronounced about the 10th day and continued to appear at intracutaneous injection sites throughout the experiment. The pyromen-treated rabbits showed the Arthus reactions initially on the 4th or 5th days. The lesions passed rapidly through the usual course, markedly exceeding those of the controls in respect to size, degree of inflammation, hemorrhage, suppuration, and necrosis. Scab formation was rapid, but in most instances scabs were resorbed rather than sloughed off as in the controls. Precipitin titers, absent in nonreacting cortisone animals, appeared earlier in the pyromen animals and were at least 50% higher than in the controls. These effects of pyromen may be correlated with its known property of stimulating the leukopoietic, phagocytic, and reticular elements of the body. (Aided by a grant from Baxter Laboratories, Inc.).

The Enzymatic Synthesis of Hypoxanthine, Inosine, and Inosinic Acid from Glycine, Formic Acid, and 4-Amino, 5-imidazolecarboxamide. MARTIN P. SCHULMAN, Ph.D., and JOHN M. BUCHANAN, Ph.D. (Dept. of Physiolog. Chem., Sch. of Med., Univ. of Penna.). Incubation of radioactive-glycine and

radioactive formic acid with homogenates and extracts of pigeon liver results in the formation of radioactive hypoxanthine, 2 moles of labeled formic acid participating for each mole of labeled glycine utilized. Radioactive-4-amino,5-imidazolecarboxamide forms hypoxanthine in the same systems, reacting approximately in equimolar proportions with formate to form hypoxanthine.

Studies have been carried out on the incorporation of labeled glycine and labeled carboxamide in homogenates to determine whether inosinic acid is an intermediate in the synthesis of hypoxanthine and inosine from these two isotopic compounds, as has been reported for formate (Greenberg, G. R., Fed. Proc. 9, 179 (1950)). Thus, inosinic acid and hypoxanthine (or inosine) were incubated with labeled substrates for short periods of time. If the hypoxanthine were formed from the carboxamide directly without prior involvement of ribose phosphate compounds, the isolated hypoxanthine or inosine should contain a greater concentration of radioactivity than the inosinic acid. Such, however, was not the case. Under the conditions of the experiment, the specific activity of the inosinic acid was 4 to 5 times greater than that of the inosine or hypoxanthine, indicating that both the elements of ribose and phosphate are added to the carboxamide prior to ring closure with formic acid, suggesting the existence of a ribotide of 4-amino,5-imidazolecarboxamide as an intermediate in purine synthesis. Radioactive glycine is likewise incorporated into inosinic acid in greater concentrations than into hypoxanthine or inosine.

When incubations are carried out in the presence of inosinic acid, the incorporation of labeled formate and glycine do not take place in the proportions predicted from *de novo* synthesis, as mentioned above. Compared to glycine, an excessive amount of formate is incorporated into the purine nucleus. Degradation of the inosinic acid isolated after incubation with radioactive formic acid showed that most of the radioactive carbon was present in the 2 position of the purine base. This excessive incorporation of formate suggests an equilibrium reaction in which inosinic acid cleaves to formate and a carboxamide ribotide, which then reacts with radioactive formate, yielding inosinate labeled in the 2 position.

These two lines of evidence indicate that a ribotide of 4-amino,5-imidazolecarboxamide is an intermediate in hypoxanthine synthesis from the carboxamide and perhaps a key metabolite in the biological formation of purines from their more elementary precursors.

Independent Biosynthesis of the Chromoproteins — Cytochrome c in Various Tissues. DAVID L. DRABKIN, M.D., Ph.D. (Dept. of Physiol. Chem., Grad. School of Med., Univ. of Penna.). By means of isotopic glycine, radioactive glycine, it has been shown that this amino acid is an important structural precursor of the hemin (iron protoporphyrin IX) of hemoglobin (Shemin, D., and Rittenberg, D., J. Biol. Chem., **166**, 621, 1946). The same hemin is present in other physiologically important chromoproteins as myoglobin and cytochrome *c*, but little decisive information is available as to their biosynthesis. In the case of cytochrome *c*, the problem is enormously complicated by the fact that, in contrast with hemoglobin, we have to deal with microquantities distributed in different amounts in practically all of the body tissues (Crandall, M., and Drabkin, D. L., J. Biol. Chem., **166**, 653, 1946).

The present report is on the comparative labeling of the cytochrome *c* of different tissues and of blood hemoglobin after the intraperitoneal administration of radioactive glycine to intact rats (controls) and to rats during liver regeneration following excision of 68%

of the liver (Drabkin, D.L., J.Biol. Chem., **171**, 395, 1947). The cytochrome *c* was isolated and determined by the method developed in our laboratory (Rosenthal, O., and Drabkin, D.L., J. Biol. Chem., **149**, 437, 1943). For handling and purification, the isolated pigment was diluted 50- to 100-fold with pure non-radioactive cytochrome *c*.

The following radioactivities (counts /min./mg.) were obtained for cytochrome *c*, C, and for hemoglobin, H: Intact rats, liver C = 715, skeletal muscle C = 196, kidney C = 428, and blood H = 118; operated rats, liver C = 2850 (at height of regeneration, 6 days after partial hepatectomy), liver C = 1039 (at 11 days after operation), skeletal muscle C = 192, kidney C = 474, heart C = 47, and blood H = 188. From the change in the activity of liver cytochrome *c* between the 6th and the 11th day after liver lobectomy, a provisional "turnover" rate of 12.7% per day for this chromoprotein in liver which has undergone regeneration may be calculated. The normal "turnover" of hemoglobin is of the order of 0.8% per day. While "turnover" rates for the cytochrome *c* in other tissues cannot be deduced from the data, the relative amounts of incorporation of radioactive carbon suggest that the "turnovers" are characteristic of the tissues but low in skeletal muscle and particularly low in heart.

The present findings demonstrate that radioactive glycine participates in the biosynthesis of cytochrome *c*, as it does in that of hemoglobin. The data permit the conclusion that cytochrome *c* is fabricated *in situ* in regenerating liver and support the tentative proposal that the biosynthesis of chromoproteins is a general property of living, aerobic cells.

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BOOK REVIEWS AND NOTICES

STUDIES ON TUMOR FORMATION. By the late G. W. DEP. NICHOLSON, Prof. of Pathology, Guy's Hospital. Pp. 637; 183 ills. London: Butterworth; St. Louis, Mo.: C. V. Mosby, 1950. Price, $15.00.

THIS book is a reprint of the 20 Tumour Studies in Guy's Hospital Reports that established Professor Nicholson's reputation as a great pathologist who could write with clarity and an urbane pen. The Reviewer cannot improve upon the words of Professor Willis, himself eminent in the field of cancer, who in the Foreword speaks of these studies as follows:

"Not only do they contain a wealth of original observations recorded with meticulous accuracy and beautifully illustrated by drawings from Nicholson's own hand, but they abound in cogent reminders that pathology is a branch of biology, in devastating and amusing criticisms of ill-founded speculations, and in apposite quotations from philosophy and the classics.

"In a letter to Nicholson acknowledging a reprint of one of his Studies in 1934, Sir Arthur Keith wrote 'there is science and poetry combined in it—to say nothing of philosophy'; and again, referring to a particularly clever play on words with which Nicholson scoffed at a piece of foolish speculation, 'you could match G.B.S. at his own game!' He who seriously reads these Studies for the first time can be assured that, along with their abundance of reliable factual information, he will find also much that is arresting, piquant and entertaining; Nicholson was a great philosopher and thought-provoker as well as a great biologist and pathological anatomist.

"The range of subjects . . . is astonishing . . . Topics which are dealt with here more authoritatively and with a stronger basis in general biology than in any other writings include the general structure of tumours, minor malformations, heterotopia of tissues, metaplasia, mixed tumours, and the teratomas. Here also are the best refutations of many false hypotheses, for example that of Cohnheim on 'cell rests', of Grawitz on renal tumours, and of Wilms on teratomas. Here is pathology written by a man with an extensive knowledge and keen appreciation of recent advances in experimental biology and embryology—who knew the work of Roux, Dreisch, Spemann, D'Arcy Thompson, Child, and Needham as well as he knew that of his fellow pathologists. Here is pathology to read and read again and ponder over."

The Reviewer most sincerely subscribes to all of this. It should be added that an excellent index now makes the contents of the Studies more readily accessible. Here indeed is a book to read not only with profit but with enjoyment. B. L.

THERAPEUTIC RADIOLOGY. By GEORGE W. HOLMES, M.D., Clin. Prof. of Roentgenology Emeritus, Harvard Med. Sch., and MILFORD D. SCHULTZ, M.D., Radiologist, Mass. Gen. Hosp., Instr. in Radiol., Harvard Med. Sch. Pp. 347; 121 ills., 10 in color. Phila.: Lea & Febiger, 1950. Price, $7.50.

THE Authors, men of wide experience and reputation in radiology, state in their preface that this book is not intended for reference or for the radiotherapist. It is aimed primarily for medical students and general physicians. For this audience, it is an admirable book, and fulfills its purpose perhaps better than any other book on the subject.

The first five chapters are specially worthy of commendation. The introductory chapter on the history of radiation therapy is most attractive, and a 30-page chapter covering the elements of radiation physics is both simple and adequate. I am unaware of any more compact and easily understood presentation of radiation physics. The biologic effects of roentgen rays and of treatment planning are also well presented. A chapter on the preparation and care of patients undergoing radiotherapy is of paramount importance not only because it is well done, but because the problems and consequences of radiotherapy are only vaguely realized by most physicians.

The details of treating the majority of disorders for which roentgen therapy is used in this country occupy the remainder of the book. One might differ in the choice of treatment plan and in the use of roentgen rays in an occasional disorder, but on the whole, the presentation is conservative, realistic, and dependable.

The numerous illustrations are of high quality, especially the color photographs of various degrees of the acute radiation reaction of the skin.

If the subject of radiation therapy is to be represented by a single volume, this book is an acceptable choice. R. R.

SIR THOMAS BROWNE, A DOCTOR'S LIFE OF SCIENCE AND FAITH. By JEREMIAH S. FINCH, Ass't. Dean of the College, Princeton Univ. Pp. 319; 18 ills. New York: Henry Schuman, 1950. Price, $3.50.

MUCH has been written about this colorful character who still evokes more interest than many more important 17th century figures. Osler's high regard for this adept in the bizarre—he always kept Religio Medici at his beside—should not be attributed in any large measure to William Osler's fondness for the quaint and roundabout, which incidentally repels many readers in the hurry of modern life. More likely is it that, while enjoying Browne's whimsical style, Osler appreciated the man's interest in all human life and thought, his underlying perspicacity, his comprehension of the basic truths in the mass of chaff, his deep concern in the midst of a busy practice with scientific progress, and his spirit of religious and poetical tolerance. All this and more is well brought out in this volume, the most recent but by no means the most exhaustive on Browne and his works.

The Author, who 15 years ago had written a Cornell dissertation on Browne's mind, works, and influence, combines matured thought with a style that is clear and, to the Reviewer, more interesting than that of his subject. There may be many who, repelled by the original texts or the more formidable compositions about Browne, will find profit and pleasure in this lighter picture, admittedly dependent on the studies of many others, which, however, are fully listed in the chapter-by-chapter bibliography of sources.

E. K.

THE ENZYMES. CHEMISTRY AND MECHANISM OF ACTION. Edited by JAMES B. SUMNER, Cornell Univ., and KARL MYRBÄCK, Biokemiska Inst., Stockholm. Vol. 1, Part 1. Pp. 724; illus. New York: Academic Press, 1950. Price, $13.50.

ENZYMOLOGY has become firmly established as an essential part of all the biological sciences, including medicine, and also of organic and physical chemistry. The great and rapid advances in enzymology during recent years have made a comprehensive survey imperative, and now this task is being accomplished through the collaboration of 78 scientists of the United States, Europe, and Australia. The work will appear in 4 parts. This Part 1 contains an Introduction by the eminent Editors in which they discuss the terminology, the general properties, and the nature and rôle of enzymes. The next 7 chapters deal with the physical chemistry of enzymes, their specificity, their relation to genes, viruses, hormones, vitamins, and chemotherapeutic drug action, the cytochemical foundations of enzyme chemistry, enzyme adaptation and enzyme inhibition, and enzymes and immunology. These chapters and the Introduction will be of particular value to the physician or biologist who wishes to obtain a thoroughly modern presentation of the more general aspects of enzymology.

The rest of the book (chapters 9 to 19) is concerned with various individual enzymes (such as the phosphatases, acetylcholine, and esterase. Each chapter has its own extensive bibliography; for example, 348 references accompany the 9th chapter, and 345 the last. An author-and-subject index will be included at the end of the 2nd and 4th parts of the treatise.

It may be said with assurance that this work will prove an indispensable guide and source of reference to many workers in all fields of biology, medicine, and chemistry.

B. L.

THE URINARY FUNCTION OF THE KIDNEY. By A. V. WOLF, PH.D., Assoc. Prof. of Physiology, Albany Med. Coll. Pp. 363; 49 ills. New York: Grune & Stratton, 1950. Price, $7.50.

THIS splendid volume should be welcomed by innumerable physiologists and clinicians. Its bibliography of 1189 references, covering all the significant contributions to the field of renal physiology, is itself of great value. The book is far more than merely a review, however. The material is presented in a critical manner, and many questionable hypotheses which have become hallowed because of oft-repetition are dealt with in a deserved fashion. No special hypothesis, much less theory, of renal function is proposed, but emphasis is placed upon a pattern of thinking which is in contrast to the classical concept. In this pattern of thought it is considered that the final aim of the kidneys is not to "clear" things, but rather that these organs are regulatory, and that "what the kidneys do represents the difference between what must be done to maintain normal living states and what is being done to this end by all extrarenal activities". Differing contentions are treated side by side in a very impartial fashion, and in those

numerous instances in which the body of evidence is inadequate to provide final answers, a very refreshing humility is evident. The clinician who has not had a great deal of training in the laboratory will find that the perusal of this book requires a great deal of concentration, but the effort expended will be generously repaid by a very significant enhancement of his understanding of the mechanisms involved in edema, in the various types of dehydration, in renal regulations, in diuresis, and in the endocrine contribution to the control of urinary function, as well as of other related subjects. It is a book heartily to be recommended for wide use among physiologists, pharmacologists, and clinicians. T. D.

ADVANCES IN INTERNAL MEDICINE. Vol. IV. Edited by WILLIAM DOCK, M.D., Long Island Coll. of Med., and I. SNAPPER, M.D., Mount Sinai Hosp., N. Y. Pp. 549. Chicago: Year Book, 1950. Price, $10.00.

VOLUME IV in the series of "Advances in Internal Medicine" is composed of comprehensive monographs, each written by a highly qualified student of the subject assigned. The topics included are: Nitrogen Mustards in the Treatment of Neoplastic Disease; Use of Radioactive Isotopes in Medicine; Brucellosis; Advances in the Neuromuscular Disorders; Use of Sodium Depletion in Therapy; Clinical Use of Anticoagulants; Hepatitis and Cirrhosis of the Liver; Hepatic Tests; and The Vascular Physiology of Hypertension.

There is a cumulative index which integrates the subject matter of this volume with the preceding three volumes. This book will be welcomed by those internists who are maintaining this series of publications and by those who are interested in a complete discussion of the subjects listed. J. L.

BACTERIAL POLYSACCHARIDES; THEIR CHEMICAL AND IMMUNOLOGICAL ASPECTS. By MARTIN BURGER, Formerly Organic Chemist Bureau of Laboratories, New York. Pp. 273. Springfield, Ill.: Charles C Thomas, 1950. Price, $6.00.

BURGER offers in this book a technical, non-critical consideration of bacterial polysaccharides. The subject matter is developed along historical lines for each of the numerous polysaccharides reviewed. The data presented are conveniently arranged, with a separate chapter allotted to each genus or species of bacteria which have been studied for the presence of immunologically active carbohydrates. Polysaccharide isolation, chemical properties, and immunological behavior, are presented with considerable detail in the well-documented text. An appendix includes procedures for the chemical separation and purification of these substances in the form of extracts of pertinent articles published by investigators in this field.

As the author mentions in the introduction, this book represents a compilation of data and only that. Immunologists and biochemists may find useful reference material here. J. F.

MEDICAL CLINICS OF NORTH AMERICA: SYMPOSIUM ON CLINICAL ADVANCES IN MEDICINE. Chicago Number. Pp. 1-298. Phila.: W. B. Saunders, Jan., 1951. Price, $15.00 a year.

THIS issue contains 20 papers which discuss a variety of subjects, including steroid therapy of arthritis, the use of radioactive iodine in diseases of the thyroid, hormones to control metastatic lesions from carcinoma of the breast, the management of lymphomas, treatment of syphilis, chemotherapy of tuberculosis, the diagnosis and therapy of multiple myeloma, chemotherapy in ulcerative colitis, and other clinical problems. The Authors present what they believe to be the best method for handling these problems. Although differences of opinion may exist, the practicing physician will not be subject to criticism if he adheres to the advice contained in these articles. H. H.

MANAGEMENT OF PERIPHERAL ARTERIAL DISEASES. By SAUL S. SAMUELS, M.D., Stuyvesant Polyclinic Hosp., New York. Pp. 345; 112 ills. New York: Oxford Univ. Press, 1950. Price, $7.50.

THE thesis of this book is conservatism in the surgical approach to peripheral arterial diseases, particularly as concerns the indications for amputation. There are many case summaries and excellent illustrations demonstrating what can be accomplished by conservative therapy in extremities which appear to be hopelessly involved. The Author's record of treating over 1000 cases of thromboangiitis obliterans with only four major amputations is an enviable one.

Other workers in the field do not share Dr. Samuels' enthusiasm for oscillometry as a precise diagnostic and prognostic aid, nor have they had his success in the treatment of occlusive vascular disease with hypertonic saline solutions. The statement that it is a

good policy to allow patients with auricular fibrillation considerable leeway with irregularity rather than to hasten return to normal rhythm by digitalis because of the danger of embolization is inaccurate, since digitalis rarely re-establishes normal rhythm. It is not understood why a chapter appears on thrombosis of the axillary vein since no other diseases of the venous system are discussed. Differential diagnostic tables would enhance the value of the book.

Despite these criticisms, this book contains much of practical value, since it reflects a vast personal experience in the handling of peripheral arterial diseases. N. L.

PRINCIPLES OF INTERNAL MEDICINE. Editor-in-Chief: T. R. HARRISON, M.D., Prof. of Medicine, Southwestern Med. School of Univ. of Texas, Dallas. Editors: P. B. BEESON, M.D., W. H. RESNICK, M.D., G. W. THORN, M.D., and M. M. WINTROBE, M.D. Pp. 1590; 245 ills; 4 color plates. Philadelphia: The Blakiston Co., 1950. Price, $12.

THIS new textbook of Internal Medicine presents many departures from the time-honored medical text format. It is quite evident from a perusal of the volume, however, that these departures provide the student and physician with a highly practical presentation of the field of Internal Medicine. An attempt has been made to integrate the pertinent content of the preclinical sciences with clinical medicine, and to approach the subject not only from the standpoint of disorders of structure, but also by way of abnormal physiology, chemistry, and disturbed psychology, an approach in keeping with modern trends in medical education. Fifty-three authors, including the five editors, have contributed to the volume. After an introduction dealing with the approach to the patient, 274 pages are devoted to a concise, pithy presentation of the cardinal manifestations of disease. This should prove to be one of the very popular features of the book since it is the approach to disease which simulates the sequence of thought processes demanded by everyday medical practice.

Physiologic Considerations are dealt with in Part II, and in this section are considered Inheritance and Aging, Principles of Neoplasia, Fluid and Electrolyte Balance, Intermediary Metabolism, Electrophysiology, and Normal Emotional Development. Part III covers Reactions to Stress and to Antigenic Substances, and Part IV, Metabolic and Endocrine Disorders. The inclusion of Nonsurgical Disorders of Bone and Muscle in the metabolic section is a departure from custom which is justified by recent advances in the understanding of these diseases. Part V deals with Disorders due to Chemical and Physical Agents, and Part VI with Diseases due to Biologic Agents. The last section of the book, Part VII, is devoted to Diseases of Organ Systems (Hematopoietic, Cardiovascular, Urinary, Respiratory, Alimentary, Hepatic and Biliary, and Nervous).

Throughout the book, the editors have been very successful in avoiding needless repetition. Rare disorders have been treated summarily by a few lines or by tabulation, or have been omitted entirely. The illustrations and diagrams are well chosen, and the bibliography is limited to a few carefully selected references, including especially some very recent publications, reviews, and monographs which contain in themselves extensive references. It is apparent that this volume will be welcomed by students and physicians as one which provides thorough familiarity with common disorders, plus an understanding of basic principles. T. D.

LIFE STRESS AND BODILY DISEASE. *Proceedings of the Association for Research in Nervous and Mental Diseases*, Vol. 29. Edited by HAROLD G. WOLFF, M.D., STEWART G. WOLF, JR., M.D., CLARENCE C. HARE, M.D. Pp. 1135; 343 ills.; 2 color plates. Baltimore: Williams & Wilkins Co., 1950. Price, $15.00.

THIS volume consists of 69 papers by different authors on various aspects of stress and the human body's reaction to it. These papers were presented at a meeting of the Association in December, 1949. They are concerned with mechanisms involved in reactions to stress; the problem of specificity in bodily reactions during stress; disorders of growth, development, and metabolism in relation to stress; and various systems of the body in relation to stress. The final chapter, entitled "Life Stress and Bodily Disease—a Formulation", is by Dr. Harold G. Wolff. W. P.

ELECTRON MICROSCOPY: TECHNIQUE AND APPLICATIONS. By RALPH W. G. WYCKOFF. Pp. 248; 202 ills.; New York: Interscience Publishers, Inc., 1949. Price, $5.00

THIS book is essentially an electron microscopist's "Vade Mecum". Its primary preoccupation is with instrumentation, technical procedure, and the myriad areas of application in the visualization of ultramicroscopic structure. The illustrations are rich, varied, technically superb; they are undoubtedly the

finest collection of pictures that have thus far been published to exhibit the applications of electron microscopy. The book is a highly individualized account of the wide experience of the author and his laboratory. As such it has the freshness and authenticity of personal experience; it suffers for the same reason from the limitations of the author's personal preference and from very inadequate assimilation and presentation of the work of other investigators of the biophysics and biochemistry of ultra-structure.

Successive chapters describe electron microscopes themselves; their adjustment and operation; preparative procedures for a) particle suspensions, b) thin sections, c) membranes and surface films, d) surface replicas, e) positive replicas, and f) atomic replicas; metal shadowing and the visualization of very small objects; the use of surface replicas; the electron microscopy of particle suspensions, including bacteria and rickettsiae; the electron microscopy of viruses; the photography of macromolecules; and the structure of macromolecular solids. The bibliography is comprehensive and is organized under topics so as to be readily usable.

Those interested in exploration of the fine-scale physical constitution of living matter, and of non-living matter as well, will find Dr. Wyckoff's book exciting and challenging reading, with a wide outlook to the future.

S. M.

AN INTRODUCTION TO PATHOLOGY. By G. PAYLING WRIGHT, M.D. Pp. 569; 231 ills. New York: Longmans, Green, 1950. Price, $6.00.

THIS book deals with the mechanisms that underlie disease processes; more specifically, it deals with causes of diseases and abnormalities, with various aspects of infection, the inflammatory reaction, reparative processes and regeneration, local disturbances of the circulation such as thrombosis, embolism, infarction, hemorrhage, and edema, with adaptations to functional requirements, with neoplasia, and with other subjects in the field conventionally known as general pathology. "A student beginning the study of medicine today is entering it at a period of unparalleled progress." It is all the more important, therefore, to give him a sound training in general principles, so that later he may be able to apply them in his study of the diseases and abnormalities of the various organs. This is the aim of the book.

It is written from a modern point of view: Emphasis is placed on the causation of disease, on pathogenesis, and on the functional disturbances that go hand in hand with structural changes. "Neither morbid anatomy nor morbid physiology can be satisfactorily studied alone; it is only when the two are brought into relation to one another that their full significance becomes apparent."

The Reviewer has read this book with interest and with pleasure. It is well written and well printed; the illustrations and the index are good; the well chosen references are a guide to further reading. It can be warmly recommended, not only to medical students but also to physicians and to the increasingly large group of workers in the various medical sciences who wish to gain an insight into the principles of pathology.

B. L.

CLINICAL ORTHOPTICS PROCEDURE. By WILLIAM SMITH, O.D., Mass. School of Optometry. Pp. 393; 70 ills. St. Louis: C. V. Mosby, 1950. Price, $8.00.

THIS book is written by an optometrist with the expressed belief that orthoptics alone can cure many of the functional defects of sight, and ocular and binocular apparatus in general. The book is dangerous in that if accepted by those without critical judgment it will expose many patients to unnecessary and frequently ill-advised eye exercises.

In the first chapter, the author states, "The treatment procedure by orthoptics is so simplified that a child of 2 years may benefit. As a matter of fact, it could be stated safely that the younger the age at which orthoptic treatment is started, the more promising may be the results."

It is works like this which have hurt orthoptics seriously.

F. A.

CHARLES DARWIN'S AUTOBIOGRAPHY WITH HIS NOTES AND LECTURES DEPICTING THE GROWTH OF THE ORIGIN OF SPECIES, and an Introductory Essay, *The Meaning of Darwin*, By GEORGE GAYLORD SIMPSON. Edited by SIR FRANCIS DARWIN. Pp. 266; 1 ill. New York: Henry Schuman, 1950. Price, $3.50.

DARWIN's great contribution to the theory of evolution has survived the many attacks upon it, renewed during the first quarter of this century, and is now secure as "one of the most significant discoveries in the history of man." Though his Autobiography and his Life and Letters had been published in 3 volumes by his son in 1888, the story has needed retelling in more compact and up-to-

date form. This has now been done, prefaced by 11 authoritative and explanatory pages, so that a satisfying and attractive picture evolves of this shrinking but persevering worker with a boundless drive to learn in spite of lifelong bouts with a painful illness, this modest but unyielding rejector of authoritarianism. Working before the science of genetics had come into being and when archeology was in its infancy, he nevertheless discovered the most important single causative factor in evolution. It should not be forgotten that his most important work bore the title, "On the Origin of Species by Means of Natural Selection".

Scientists, no matter in what field they may be engaged, have much to learn from this patient student who worked for 20 years, developing and checking on his theory, before publishing. A man of complete intellectual honesty, he always sought for the truth rather than for support of his theories and welcomed, even sought out, criticism from his colleagues. The undeserved abuse heaped upon him he received undisturbed and without rancor. His abhorrence of superiority "and his generosity in attributing credit to others" give further support to the epithet "A Saint in Science".

This volume is unquestionably one of the best in the valuable Life of Science Library series. E. K.

NEW BOOKS

Child Psychiatry in the Community. By HAROLD A. GREENBERG, M.D., Senior Staff Psychiatrist, Inst. for Juv. Res., Chicago, JULIAN H. PATHMAN, HELEN A. SUTTON, R.N., and MARJORIE M. BROWNE, M.A., Pp. 296. New York: G. P. Putnam's Sons, 1950. Price, $3.50.

THIS book outlines present-day thinking as developed through experience in a large clinic which was one of the pioneers in child psychiatry. It is designed for teachers, nurses, and others who have children in their care and aims to acquaint the members of these professions with the inner workings of a child guidance clinic and to illustrate with cases and examples the types of problems seen and the methods used in treatment. W. P.

Emotions and Clinical Medicine. By STANLEY COBB, M.D., Bullard Prof. of Neuropathol., Harvard Med. School. Pp. 243; 19 figs. New York: W. W. Norton & Co., 1950. Price, $3.00.

THIS book brings together the new knowledge concerning emotions, the brain, and the body. Anatomy of the brain and emotional and social psychiatry are considered. It reflects the great amount of thought that the scholarly author has given to these matters and has greater value as a contribution to theoretical psychiatric literature than as a book with practical clinical applications. W. P.

A GUIDE TO PSYCHIATRIC BOOKS *with a Suggested Basic Reading List. The Menninger Clinic Monograph Series* No. 7. By KARL A. MENNINGER, M.D., Gen. Dir., Dept. of Education, Menninger Founda., and GEORGE DEVEREUX, Ph.D., Lecturer in Anthropology, The Menninger School of Psychiatry and Topeka Institute for Psychoanalysis. Pp. 148. New York: Grune & Stratton, 1950. Price, $3.50.

THIS guide book consists of two parts. The first, entitled "A Guide to Psychiatric Books", is composed of a list of 1193 books relating to Psychiatry and related fields. Part 2, entitled "Suggested Basic Psychiatric Reading List", consists of a list of 89 of the most significant books in the field which might be considered indispensable basic reading for all psychiatric residents. W. P.

Your Prostate Gland—Letters from a Surgeon to his Father. By REED M. NESBIT, Prof. of Surgery, University of Mich. Med. School; Chief, Sect. on Urol., Univ. Hosp., Ann Arbor, Mich. Pp. 50; 6 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

THIS brief book, written for the layman, gives a simple but competent description of both benign and malignant prostatism, its symptomatology, pathology, diagnosis, and treatment. The author, who heads one of the largest transurethral resection centers in the country, is admirably impartial in discussing closed and open surgery as methods of treatment. This book is recommended as reading material for the patient who is a candidate for prostatic surgery. K. C.

Advances in Carbohydrate Chemistry. Vol. V. Edited by CLAUDE S. HUDSON, National Institutes of Health, Bethesda, Md., and SIDNEY M. CANTOR, American Sugar Refining Company, Philadelphia, Pa. Pp. 322. New York: Academic Press, 1950. Price, $6.80.

THIS fifth annual volume of reviews of selected topics in CHO chemistry maintains the excellent character of previous issues. Ten topics are reviewed: applications in the Carbohydrate Field of Reductive Desulfurization by Raney Nickel; Enzymes Acting on Pectic Substances; The Relative Crystallinity of Celluloses; The Commercial Production of Crystalline Dextrose; The Methyl Ethers of D-Glucose; Anhydrides of the Pentitols and Hexitols; and Xylan. Of more strictly biochemical interest are the reviews by W. Z. Hassid and M. Doudoroff: Enzymatic Synthesis of Sucrose and Other Disaccharides; A. Gottschalk: Principles Underlying Enzyme Specificity in the Domain of Carbohydrates; and M. L. Caldwell and M. Adams: Action of Certain Alpha Amylases. H. V.

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